A novel, non-invasive, optical device for the measurement of total haemoglobin and stroke volume, and for the identification of fluid responsiveness – initial clinical evaluation

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Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

Signed

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Dr. Alan Jonathan Broderick

Buíochas/Nga mihi

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Summary

Haemoglobin is a molecule present in red blood cells and is essential for adequate oxygen delivery to tissues. It is measured frequently in many clinical situations, particularly intraoperatively. Until recently, it was only possible to measure haemoglobin through blood testing which is an invasive process and requires some time to process. Devices have been developed in the last number of years to minimise both the invasiveness and time needed to measure haemoglobin. More recently, devices are available that provide instant or continuous results without requiring blood samples but these have not been universally accepted into clinical practice.

Stroke volume is the amount of blood ejected from the heart at each heartbeat, and is one of the determinants of cardiac output (which is also responsible for ensuring adequate tissue oxygen delivery). It varies across many clinical states, particularly following major haemorrhage or reduced cardiac function. The analysis of variations in stroke volume during the respiratory cycle (i.e. between the end of a complete exhalation and the end of the following complete exhalation) has been shown to predict when a patient's stroke volume could be improved by administering intravenous fluid. Successfully identifying such 'responders' can lead to earlier appropriate treatment, and also avoid over-treatment.

However, at present the most reliable methods of measuring stoke volume or predicting fluid responsiveness involve the use of invasive devices which have the potential to be harmful.

A novel device has been developed which uses the absorbance of red and near-infrared light across a finger tip as the basis for the measurement of both haemoglobin and stroke volume, along with the prediction of fluid responsiveness. This is non-invasive and would allow for the continuous measurement of these physiological parameters, with potential for more efficient and timely treatment.This thesis presents the first clinical evaluation of the two functions of this novel device across three studies.

The first study investigated the measurement of haemoglobin by this device across twenty five patients undergoing heart surgery who each underwent four samples. The second study looked into the measurement of haemoglobin in one hundred pregnant women during their twenty-week antenatal clinic visit. In both studies, the results from the device were compared with the standard laboratory method of measurement. The third study investigated the device's ability to measure stoke volume and to predict fluid responsiveness in twenty patients undergoing heart surgery.

The results of these studies showed that the device is currently not suitable for use in clinical practice as a replacement for the more established methods of measurement one each case. Some explanation is offered regarding the poor results.

1.Introduction

1.1.Thesis application and proposal

The application for MD degree by thesis in Anaesthesia and Intensive Care Medicine was approved by the Faculty of Medicine at University College Cork in October 2011.

There is a change to the analyses performed on the data collected during the third clinical trial ("Evaluation of a novel, non-invasive method for the estimation of stroke volume and the prediction of fluid responsiveness."). It was not possible to construct both Bland-Altman and polar plots as initially planned, as to do so would require the novel device to output in units equivalent to those of the reference technique, which is not the case. In addition, a receiver operating characteristic (ROC) curve was constructed in order to analyse the ability of the novel device to predict subjects' responsiveness to the administration of intravenous fluids. This is further documented in the discussion section of chapter 4.

1.2. Perioperative photoplethysmography – history and recent developments

Intraoperatively, it is routine to monitor blood pressure, heart rate, oxyhaemoglobin saturation, respiratory rate, end-tidal oxygen and carbon dioxide partial pressures, and the electrocardiogram. During major surgery, more advanced and increasingly invasive monitoring can be instigated, such as intra-arterial blood pressure, central venous pressure, and transoesophageal echocardiography. Blood sampling is currently necessary to measure plasma haemoglobin concentration.

Ideally, these physiological variables would be measured continuously and non-invasively. The following is a list of the ideal characteristics of such a monitor:

- Non-invasive (no blood sampling or intra-vessel catheterisation would be necessary)
- Accurate
- Reliable
- Fast (minimal time delay between commencement of monitoring and the displayed result)
- Continuous (allowing the identification of trends in evolution)
- Free from artefacts (such as motion or external light sources)
- Electrically safe (no direct harm from the device to the patient)

- Requires minimal skill to operate
- Easily interpretable results
- Robust
- Portable
- Economically advantageous (reusable, inexpensive capital expenditure, indirect savings from decreased use of single-use items and laboratory equipment)
- Improved patient outcomes

Photoplethysmography (PPG) has met many of these characteristics already, specifically in relation to oxyhaemoglobin monitoring. However, new applications of PPG continue to be discovered with the potential for improved patient outcomes and cost savings. This chapter reviews the history of the development of PPG and the expanding applications of this technology relevant to the anaesthetist in the intraoperative setting.

1.3.The beginnings of photoplethysmography

'Plethysmography' derives from the Greek words 'plethysmos', meaning 'to increase' and 'graphos', meaning 'something drawn or written'[1]. In medical research and clinical use, a plethysmograph can be described as an instrument that can measure changes in volume over time[2]. PPG is the analysis of changes in the volume of blood passing through a region of the body using the variable absorption of specific wavelengths of light between a light source and a detector[3]. Two types of PPG are used – reflective PPG and transmission PPG. Reflective PPG refers to positioning of the detector next to the light source and measures the absorption of backscattered light with changes in blood volume. More commonly, transmission PPG is used, whereby the light source and detector are placed opposite each other across the region to be studied. Alrick Hertzman reported the development of transmission PPG in 1937[4] and described the relationship in humans between blood volume changes recorded by reflective PPG and those recorded by mechanical plethysmography the following year[5].

In the 1940s Hertzman and his colleague John Dillon found the PPG waveform to be made up of two main components, which are now known as AC and DC[6]. The DC component represents light absorption due to venous and non-pulsatile arterial blood, along with that due to

the various body tissues[3]. The AC component represents the variation in light absorption caused by the temporary increase in blood volume of the sample region due to arterial pulsation. Modern PPG equipment can usually display only the AC component of the signal[1].

Although much of the research into PPG has led to advances in the assessment of vascular diseases[7] and autonomic function[8], this review will focus on the perioperative use of PPG to monitor physiological functions that can benefit the anaesthetist in the safe management of the patient in the operating theatre. PPG can also be used to non-invasively monitor respiratory rate, but as alternative methods are available for this purpose in the perioperative environment, this application of PPG will not be considered here.

1.4. Pulse oximetry and heart rate monitoring

Karl Matthes was the first to describe the measurement of oxyhaemoglobin saturation in a human by comparing the absorption of light of two wavelengths (red and green) at the ear[9]. World War II and the expanding role of the air force accelerated interest in the non-invasive monitoring of oxyhaemoglobin saturation. As fighter planes were unpressurised, pilots would frequently lose consciousness at higher altitudes due to hypoxia. This led to American researcher Glenn Millikan's 1942 publication in which he described a lightweight device for measuring oxyhaemoglobin that fitted over the ear (based on Matthes' prior work) and coined the term "oximeter"[10]. Unfortunately, Millikan's oximeter was not very helpful in aviation as it was very susceptible to motion-artefacts. Meanwhile, J Squire in London developed a device which first squeezed the blood out of a web space of the hand and measured absorbance using red and infrared light for zero calibration, and then again with blood flow restored[11]. His work is considered the immediate forerunner of modern pulse oximetry[12]. Earl Wood improved upon Squire's idea by modifying Millikan's device for the ear to include a compression system and also an improved infrared filter[13]. Wood's newer system went on to be used clinically but was not very reliable.

In the early 1970s, at the Research Division at Nihon Kohden Corporation, Japan, Takuo Aoyagi ran into difficulties attempting to use a similar technique to Wood's to measure cardiac output at the ear using a dye densitometry method. An artefact caused by arterial pulsation interfered with the dye dilution curves obtained. Thinking back to the earlier studies of oximetry, Aoyagi realised that periods between this 'noise' could be used as zero calibration against the arterial pulsation and so he conceived the principle upon which pulse oximetry is now based. Subsequently, he chose the wavelengths 630 nm and 900 nm for transmission PPG and calculated the "ratio of ratios" (the ratio of AC/DC intensity for each wavelength, and then the ratio of these). This ratio correlated well with arterial oxyhaemoglobin saturation[14]. Nihon Kohden failed to develop Aoyagi's system further, and so the first commercially available pulse oximeter became Minolta's OXIMET MET-1471 in 1977. As miniaturisation allowed for smaller devices, including the use of cheaper and more versatile light-emitting diodes (LEDs), pulse oximeters began to be used by anaesthetists in operating theatres. An anaesthetist working at Stanford University, William New, had noticed that colleagues would borrow pulse oximeters (normally kept in the respiratory laboratories) for use during particularly complex cases and he sought to capitalise on this phenomenon by setting up Nellcor in 1981. Nellcor released their pulse oximeter (the Nellcor N-100) in 1983, which was the first device to introduce a sound to accompany each detected pulse

along with a clear change in pitch as oxygen saturation varies. It therefore also gave measured heart rate. The first published evaluation of the Nellcor N-100 was written by New himself[15].

Although the renowned anaesthetist, academic and historian J W Severinghaus noted that the introduction of pulse oximetry coincided with a 90% drop in intraoperative mortality[12], major studies have not proven this association to be true[16]. Indeed, the most recent Cochrane Review on the subject concluded that "despite an intense methodical collection of data from a relatively large general surgery population, … the value of perioperative monitoring with pulse oximetry is questionable in relation to improved reliable outcomes, effectiveness and efficiency"[17]. Nevertheless, pulse oximetry is today considered essential for the safe conduct of anaesthesia and is acknowledged as a minimum standard for the monitoring of oxygenation by many professional bodies[18-20].

1.5. Plasma haemoglobin concentration

Oxygen delivery to tissues is dependent upon plasma haemoglobin concentration (Hb), oxygen and cardiac output and may be calculated using the equation:

$$\text{Oxygen Delivery} = [1.39 \times Hb \times SaO_2 + (0.023 \times PaO_2)] \times CO$$

where

SaO_2 = arterial oxyhaemoglobin saturation (percentage of total haemoglobin that is oxygenated)

PaO_2 = partial pressure of oxygen in arterial blood (kilopascals)

CO = cardiac output (litres/minute)

The lower limit of normal of Hb is generally accepted as 130 $g.l^{-1}$ for males and 120 $g.l^{-1}$ for females[21], and large intraoperative decreases in Hb (to levels as low as 70 $g.l^{-1}$ for example) can result in up to a 50% decrease in oxygen delivery to tissues. As tissue hypoxia can lead to organ dysfunction or failure, it is clear that monitoring of Hb must be an important focus of perioperative patient management. Indeed, laboratory blood testing is carried out an estimated 4-5 billion times per year in the United States[22], with the estimation of plasma haemoglobin (Hb) concentration making up over 400 million of these tests[23].

Preoperative anaemia is known to be associated with worse outcomes, including an increased risk of mortality, longer hospital length of stay, increased frequency of intensive care admission and increased frequency of requirement for post-operative ventilation[24, 25]. It is possible that the treatment of pre-operative anaemia can mitigate these risks. Intraoperatively, Hb may fall due to blood loss or haemodilution from intravenous fluid administration leading to the need for blood transfusion. Hb monitoring may also identify bleeding not otherwise apparent leading to location and treatment of the cause. Higher postoperative Hb is associated with fewer readmissions[26].

Patients undergoing cardiac surgery experience large changes in Hb due to major blood loss, haemodilution (particularly on the instigation of cardiopulmonary bypass) and the likely administration of blood products. Major bleeding in cardiac surgery was shown to be independently associated with operative mortality in one study. In addition, the same study also found that preoperative anaemia and blood transfusion were also associated with operative mortality[27]. Frequent Hb estimation is therefore an important feature in the perioperative management of major surgery such as cardiac surgery.

According to the World Health Organisation, 18% of pregnant women in industrialised countries are anaemic[28]. It is likely that this prevalence is

higher in developing countries where proximity to suitable laboratories limits accurate testing. Iron-deficiency anaemia in pregnancy is associated with lower birth weight due to increased rates of pre-term birth although studies have not yet conclusively demonstrated that iron supplementation leads to improved clinical outcomes[29]. Nevertheless, as it is considered unethical to not treat antenatal anaemia, identifying anaemia remains an important part of antenatal screening.

The laboratory gold standard for plasma haemoglobin estimation is the cyanmethaemoglobin method (HiCN)[30]. As this method involves the use of the highly toxic reagent potassium cyanide, cyanide-free methods are now more common in the clinical setting with device such as the Sysmex XE-2100 (Sysmex Corporation, Kobe, Japan)[31]. The newer automated methods can use combinations of flow cytometry and fluorescence to estimate Hb and can also obtain further information such as differential cell count. However, there can be significant delays in transporting blood samples to laboratories, with further delays involved both in processing the sample and in providing clinicians with the result, which can lead to late treatment in emergency situations.

Arterial blood gas analysis machines can be used as point-of-care devices to provide a more rapid estimation of plasma haemoglobin, but the results must be used with caution as the limits of agreement between

these and laboratory-based estimations can be wide[32]. A handheld device for point-of-care measurement of plasma haemoglobin, the HemoCue (HemoCue, Ängelholm, Sweden) has been available for many years but can underestimate the true value of plasma haemoglobin and some authors recommend against using the HemoCue as a full replacement for laboratory-based estimation[33, 34].

The above methods involve the sampling of blood which can be painful for the patient and includes the risks of infection and of accidental needlestick injury to the proceduralist. Although rare, repeated blood sampling can lead to anaemia[35] particularly in neonates (although this risk is not likely with the HemoCue).

1.6.Non-invasive, continuous haemoglobin measurement

None of the above methods allow a continuous means of monitoring plasma haemoglobin concentration. Continuous monitoring in the operating theatre would allow the anaesthetic and surgical teams to identify trends in haemoglobin concentration due to haemodilution or blood loss and initiate earlier treatment[23]. In the case of pulse oximetry, it was the real-time, continuous and non-invasive nature of the device that allowed anaesthetists to identify when arterial oxygen saturation was falling before it had become clinically dangerous[36]. A continuous, non-invasive Hb monitor might prove to be similarly useful.

Sysmex Corporation (Kobe, Japan) launched the Astrim in 1999, which was the first device to utilise PPG for the continuous and non-invasive measurement of Hb[37]. This device used a charge-coupled device camera to detect light of wavelengths 660, 805 and 880 nm shone through a fingertip. Kinoshita et al were the first to investigate this device in 2002. The investigators found a good correlation between the novel device (Astrim, Sysmex Corporation, Kobe, Japan) and a laboratory reference ($r=0.896$) in healthy volunteers, but poor correlation in a group of patients with multiple myeloma ($r=0.488$)[38]. They did not present figures for bias (mean of the differences between the paired samples of the

methods of measurement) or limits of agreement as per the Bland-Altman method for assessing agreement between methods of measurement[39]. Saigo et al later investigated the effect of the presence of white blood cells and platelets on the performance of the Astrim (ex-vivo and in-vivo) and found that the results were unaffected[37]. Despite this promising start, the Astrim was not accepted into clinical use for Hb measurement. This is likely due to its large size and a design which would not be conducive to intraoperative use. In the meantime, Sysmex appear to have developed the Astrim system for use by athletes in a non-clinical setting.

Noiri et al in 2005 described the use of a device manufactured and patented by Nihon-Kohden (the company behind Takuo Aoyagi's original pulse oximeter), and found the bias between the non-invasively recorded Hb and the laboratory-determined Hb to be 0.00 $g.l^{-1}$ and -1.6 $g.l^{-1}$ in each of their patient groups with r^2=0.81 and 0.75 respectively[40]. This device used four wavelengths (660, 805, 940 and 1300 nm) instead of the Astrim's three. No further published investigations into this device appeared until 2013 when Toyoda et al concluded that the device could not replace laboratory Hb measurement and that it could not be used for decision-making in relation to blood transfusion[41]. It is not clear as to why Nihon-Kohden appear to have abandoned development of this device, although it should be noted that Nihon-Kohden announced an

expanded licensing agreement with Masimo in December 2008 which saw some integration of both companies' monitoring devices.

An alternative device called the NBM-200MP (OrSense, Nes Ziona, Israel) received FDA approval in 2010. The device operates using the principle of occlusion spectroscopy and consists of a ring-shaped probe containing a pneumatic cuff that fits over the base of a finger. In order to measure Hb, the cuff inflates to just above systolic blood pressure which temporarily occludes blood flow in the finger. The different absorption of light of various wavelengths between 600 and 1500 nm before and after occlusion allow the calculation of Hb. However, it takes 90 seconds to determine Hb each time, and therefore cannot truly be said to be continuous. Despite this, the device could potentially find an application in intraoperative care. The first clinical evaluation of the NBM-200MP to be published in peer-reviewed literature appeared in early 2012[42]. For the purposes of this review, 9 trials were identified (as of 19th March, 2020) which carried out clinical evaluations of the NBM-200MP compared to laboratory reference methods, and these are summarised in Table 1. Two of these trials did not report the limits of agreement between the methods of Hb measurement[43, 44]. The study by Coquin et al[45] was stopped early following an interim analysis due to the poor performance of the device in patients admitted to an intensive care unit with gastrointestinal bleeding. The remaining studies reported broad

limits of agreement, which calls into question the clinical usefulness of the NBM-200MP. Importantly, none of the studies evaluated the use of the device in the intraoperative setting.

Masimo Corporation (Irvine, California, USA) first introduced non-invasive Hb monitoring in 2008, and the technology is now incorporated into two devices; the Radical-7, a bedside monitor; and the Pronto-7, a handheld monitor. Of these, only the Radical-7 offers continuous Hb monitoring. Either device functions via PPG using greater than seven wavelengths of light (Masimo have not published the exact number of wavelengths, nor the precise wavelengths used).

The first evaluation of the Radical-7 was described in an abstract in 2007[46], and interest gradually increased with more and more agreement studies between the Radical-7 and various reference devices being published. This culminated in a systematic review and meta-analysis of non-invasive Hb monitoring devices by Hiscock et al, which included 18 studies of the Radical-7, 6 of the Pronto-7, and 19 studies of various HemoCue devices[47]. The authors found no bias in the Masimo devices and a small fixed bias of 5.3 $g.l^{-1}$ in one of the HemoCue devices. However, the limits of agreement for both Masimo devices (approximately ±30 $g.l^{-1}$) were quite large, limiting their usefulness as an independent guide to blood transfusion decision-making. In a first of its

kind study, published after Hiscock et al's systematic review, the use of the Radical-7 in orthopaedic surgery was associated with a 4% reduction in the risk of a patient receiving an intraoperative blood transfusion[48]. If this trend was borne out by further studies, it may lead to patient benefits resulting from reduced potential for the ill effects of transfusion, as well as reduced overall healthcare costs. However, Galvagno et al found that the Radical-7 "did not enhance the ability to predict the need for blood transfusion" in trauma patients, when added to the combined measures of age, sex, pre-hospital heart rate, SpO_2, and admission heart rate[49]. Indeed, one study found a potential "error" incidence of 13% (defined as where the Radical-7 gave a Hb measurement of ±10 $g.l^{-1}$ where the reference value was <90 $g.l^{-1}$); this could lead to transfusion where none was required, or the withholding of necessary transfusion[50]. Further, there is evidence to suggest that the performance of the Radical-7 worsens as a patient's perfusion state worsens (as may occur in critically ill patients)[51], which would suggest caution in the intraoperative use of this device in any patient suffering from shock, or in cardiac (or other major) surgery where patients are more likely to require the use of vasopressors following separation from cardiopulmonary bypass.

There has been much commentary on Masimo's devices in the published literature. Morey at al argue that a fundamental problem with most of the method comparison studies published to date is their tendency to mostly

feature data pairs where the reference Hb is above the range 60-100 $g.l^{-1}$, values which may not trigger a "decision to transfuse"[52]. Clearly, an error of ±30 $g.l^{-1}$ as per the review by Hiscock et al[47] is far less a problem where a patient's true Hb is 120 $g.l^{-1}$ than if it was 60 $g.l^{-1}$.

More recently Barker et al[36] have suggested that these devices' real value lies in their ability to monitor the trend in Hb, rather than the absolute value per se. Monitoring Hb trend would allow the anaesthetist to "(a) detect decreasing Hb when it is assumed to be stable; (b) identify stable Hb values when they are assumed to be decreasing; and (c) identify increases in Hb when they are assumed not to be increasing". This may prompt the anaesthetist to carry out a laboratory Hb measurement sooner in the case of a downward trend on the monitor and take further action as appropriate. Barker and colleagues also make the case that as up to 31% of transfusions in operating theatres are carried out in the absence of formal Hb results, clearly there are occasions when there simply isn't enough time to wait for a laboratory result. In these situations, a continuous monitor may either provide reassurance that there is enough time to send a blood test, and possibly avoid a transfusion, or indicate instead that a transfusion will be necessary immediately.

As Morey and Rice's papers concluded[52, 53], further study into the performance of these devices in the critical Hb range of 60-100 $g.l^{-1}$ will need to be made, along with alternative measures of agreement such as those suggested previously by Clarke in relation to glucose monitors (error grid analysis)[54]. In the future, from an anaesthetist's perspective, the most important marker of how well continuous non-invasive Hb monitoring performs will be how reliable our decisions regarding blood transfusion will be. For now, trending patterns can help raise the possibility of transfusion, but do not replace laboratory Hb measurements.

1.7. Fluid responsiveness

Intraoperatively, patients may require the administration of intravenous (IV) fluids in order to increase cardiac preload (left ventricular end-diastolic volume) and subsequently improve cardiac output and blood pressure. IV fluids are also administered in the setting of circulatory or septic shock. However, patients will only respond to fluid administration if their myocytes are operating on the ascending portion of the Frank-Starling curve[55]. It is also well known that patient outcomes are worsened if excessive fluid is administered[56], and so there is a need to establish in advance whether or not a patient is likely to respond to a fluid bolus. Traditional measures, such as central venous pressure (CVP), have been shown to be unhelpful in identifying those patients who would benefit from fluid administration[55]. Echocardiography can be useful but is not always available or practical and requires a skilled operator. A method of non-invasively assessing fluid responsiveness would allow for more timely intervention with minimal harm to the patient.

1.8. Pulse oximetry plethysmographic variation and Plethysmographic Variability Index as monitors of fluid responsiveness

Mechanical ventilation is well known to cause haemodynamic changes in patients. In particular, as intrathoracic pressure increases during positive-pressure ventilation (PPV), venous return to the heart is decreased, with a subsequent decrease in left ventricular stroke volume[57]. This decrease in stroke volume leads to a decrease in systolic blood pressure.

Coyle et al first attempted to quantify the decrease in systolic blood pressure with PPV in 1983, by calculating the difference between the maximum and minimum systolic blood pressures over a single respiratory cycle. They called this the 'positive pressure paradox' and found that this value decreases when fluid is administered to hypovolaemic patients[58]. They also investigated Δ up and Δ down, the differences between the baseline (i.e. end-expiratory) systolic blood pressure and maximum and minimum systolic blood pressures respectively. Perel et al[59] later suggested the name 'systolic pressure variation' (SPV) in place of Coyle's 'positive pressure paradox' and investigated this phenomenon more formally during graded haemorrhage in dogs. Coyle demonstrated that SPV and Δ down rose as cardiac output fell.

These studies involved the use of invasive arterial catheters, which apart from causing discomfort on insertion, are associated with complications[60]. With the knowledge that the PPG is technically a measure of blood volume passing through a specific region over time, Partridge et al became the first to describe the use of the PPG to measure what they termed 'pulse waveform variation' as the maximum variation in the peaks of the PPG waveform as measured on printouts of the (highly processed) PPG. As the PPG waveform has no units, they simply measured the maximum variation in the peaks of the waveform on printouts from their monitor and called this 'pulse waveform variation'. They showed that this variation correlated with the SPV in a series of 12 patients undergoing major surgery[61]. These findings were confirmed in 1999 by Shamir et al's investigation of the relation between SPV and PPG variation in a controlled haemodynamic setting[62].

Meanwhile, in the same year a group led by Michard suggested a novel dynamic index of volume status based on the arterial waveform called 'pulse pressure variation' (PPV) calculated from the formula:

$$PPV\ (\%) = 100 \times ((PP_{max} - PP_{min}) / ((PP_{max} + PP_{min}) / 2))$$

where PPmax and PPmin were the maximal and minimal pulse pressures measured over a respiratory cycle[63]. They went on to demonstrate that

PPV was superior to SPV as an indicator of fluid responsiveness[64]. Monitoring and minimising PPV with an intraoperative fluid management protocol was later shown by Lopes et al to result in a decreased length of hospital and intensive care unit stay, and reduced rate of complications[65].

In 2005 Cannesson et al published the details of a new method of measuring the variation in the pulse oximetry plethysmographic waveform (ΔPOP), which was calculated by substituting the equivalent terms from the PPG into the formula for PPV. Also known as pulse oximetry plethysmographic variation (POPV), this new measure of volume status correlated well with PPV in patients with circulatory failure[66]. Unfortunately, as POPV could not be measured automatically the results were only available post hoc. Cannesson later became the first to investigate "Pleth Variability Index" (PVI), which is a proprietary measurement developed by Masimo. Cannesson first evaluated PVI in 2008, and its calculation derives from the Perfusion Index (PI):

$$PI = (AC/DC) \times 100$$

where AC and DC refer to the varying and fixed portions of light absorption respectively.

PVI is then calculated using a slight variation on the formula used for POPV:

$$PVI = ((PI_{max} - PI_{min}) / PI_{max}) \times 100$$

where PI_{max} and PI_{min} are the maximal and minimal PI recorded over a respiratory cycle respectively.

Cannesson showed that PVI was potentially useful as a measure of POPV and correlated well with PPV[67]. Assuming that the DC portion of the signal remains constant over a single respiratory cycle, the only difference between POPV and PVI is that they measure percentage difference and percentage change respectively.

Interest in the usefulness of these non-invasive predictors of fluid responsiveness has continued with a recent systematic review and meta-analysis concluding that both methods are reliable predictors of responsiveness to fluid boluses of at least 500 mL but are not as useful with smaller boluses[68]. However, none of the included studies were randomised-controlled trials, and only 6 studies were included evaluating POPV, 3 studies with PVI and one study which looked at both (for a total of 233 patients). Further, no children were included, as were few patients receiving noradrenaline, which means the results cannot be extrapolated

to these groups. The most important weakness of Sandroni's meta-analysis, however, is that no clinical outcome data was considered. Forget et al have demonstrated reduced lactate levels in patients undergoing major abdominal surgery managed with PVI-guided fluid administration, but no improved clinical outcomes[69]. They stated that this result confirmed Lopes' conclusion, which is not correct; reduced lactate levels are not the same as reduced lengths of stay or complication rates. As with any new medical device technology, improved patient outcomes will be the ultimate test of whether POPV or PVI has a role in perioperative medicine.

POPV and PVI have further limitations. As yet there is no commercially available automated POPV monitor and consequently it cannot be shown whether this measurement would perform better than PVI in improving patient outcomes. While they may be helpful in identifying patients who will respond to a fluid bolus, they are less helpful in predicting the magnitude of response[68]. As PPV is not helpful as a predictor of fluid responsiveness in spontaneously breathing patients[70], it is likely that PPG will be unhelpful in such patients also. As anyone who has clinical experience with pulse oximetry will know, motion artefact can be a major drawback with PPG. PVI has been shown lose its ability to discriminate between responders and non-responders in patients with a lower peripheral perfusion state[71]. Factors known to affect pulse oximetry such

as hypothermia and poor peripheral perfusion[72] would also presumably interfere with PVI. Given that arrhythmias result in great variation of the left ventricular end diastolic volume (and therefore stroke volume) one would expect this to interfere with both POPV and PVI. Finally, noradrenaline limits the ability of PVI and PPV to predict fluid responsiveness in intensive care patients[73], which may limit the usefulness of PVI in this setting.

Given that there is no automated POPV device available, it cannot be shown whether this measurement would perform better than PVI in improving patient outcomes.

1.9.Conclusion

Photoplethysmography has the potential to fulfil new roles in the operating theatre. Pulse oximetry was rapidly and widely adopted for several reasons; it was reliable, non-invasive, portable, easy to interpret, and the treatments for low SpO_2 were easy to instigate quickly with minimal risk of harm to the patient. Precise accuracy was not as clinically important as the trend of the SpO_2 in most clinical situations.

However, the newer applications of PPG may not be adopted into routine clinical practice as easily as pulse oximetry, for several reasons. In patients undergoing major surgery, the failure to transfuse blood appropriately can cause harm to the patient, either in the case of omission or over-treatment, and the economic cost may be significant in either case. The adverse effects of blood transfusion are well known and can include allergic reactions, haemolytic transfusion reactions (from donor-recipient mismatch), transfusion-related acute lung injury, transfusion-related circulatory overload, bacterial, viral or prion contamination and transfusion-related graft-versus-host disease[79]. Introducing non-invasive haemoglobin monitoring into the operating theatre has been shown to decrease the usage of donated blood. A study conducted in Spain demonstrated a reduction in 20 transfusions across 127 patients undergoing hip trauma surgery with non-invasive

continuous Hb monitoring, compared with 122 similar patients without such Hb monitoring. This amounted to a saving per patient of €20.59, which could be extrapolated to a national saving of €1.736 million per year were such monitoring to be introduced nationally[80].

Where major bleeding or fluid shifts are anticipated, most anaesthetists currently closely monitor Hb via frequent blood sampling (either using a blood gas analyser or formal laboratory testing). This raises the question of whether or not non-invasive haemoglobinometry can identify patients requiring a blood transfusion, in whom timeliness is critical, at an earlier stage thus making a real clinical difference. Some benefit in reducing blood loss may be expected from the avoidance of repeated blood sampling, but in the face of surgical blood losses these gains may be clinically insignificant in the operating theatre. In the case of fluid bolus administration, PVI does not currently perform well in patients with low perfusion states or who are receiving noradrenaline, the very patients in whom fluid administration is often most clinically important. Clear and reliable reference values will be needed along with a guarantee of continuous performance before PPG will be accepted into routine use.

Due to the limitations described above, these new monitors run the risk of becoming just more "noise" in the operating theatre, unless they are proven to reliably signal the need for treatment and monitor the

response to treatment. More importantly, their use must be demonstrated to lead to better clinical outcomes in relevant patient groups.

1.10. Tables

Table 1. Summary of studies evaluating the NBM-200MP (OrSense, Nes Ziona, Israel)

Study First Author	Year	Subjects	Patients (comparisons)	Reference device	Correlation coefficient
Gayat[42]	2012	Emergency patients	297 (297)	ADVIA 2120 (Siemens)	N/A
Pinto[43]	2012	Blood donors	205 (205)	CellDynRuby (Abbott)	N/A
Hadar[74]	2012	Pregnant women	63 (126)	LH750 (Beckman Coulter)	r=0.82
Kim[44]	2013	Blood donors	506 (506)	LH500 (Beckman Coulter)	r^2=0.472
Belardinelli[75]	2013	Blood donors	445 (445)	AcT-5 diff (Beckman Coulter)	N/A
Coquin[45]	2013	Unstable patients	34 (135)	LH780 (Beckman Coulter)	r=0.5 (thumb) r=0.3 (index finger)
Singh[76]	2015	Blood donors	485 (485)	KX-21 (Sysmex)	N/A
Mallhi[77]	2016	Blood donors	500 (500)	KX-21 (Sysmex)	r=0.5099
Rout[78]	2019	Blood donors	1082 (1082)	ORION 60 (Ocean Medical Technology)	r=0.726

Study First Author	Bias Hb ($g.l^{-1}$)	Precision ($g.l^{-1}$)	Limits of agreement		Laboratory Hb range ($g.l^{-1}$)
			Lwr ($g.l^{-1}$)	Upr ($g.l^{-1}$)	
Gayat[42]	2.1	N/A	-30.1	34.2	121-142
Pinto[43]	N/A	N/A	N/A	N/A	111-179
Hadar[74]	1	8.6	-15.9	17.9	69-139
Kim[44]	N/A	N/A	N/A	N/A	N/A
Belardinelli[75]	2.9	9.8	-16.4	22.1	N/A
Coquin[45]	-4	16	-35	43	N/A
Singh[76]	-6.6	N/A	-33.9	20.9	N/A
Mallhi[77]	3	8.39	-22	28	99-197
Rout[78]	-8.9	N/A	-29.9	12.16	68-203

Hb = Haemoglobin

Lwr = Lower

Upr = Upper

N/A = Not Available

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2.The Novel Device

2.1.Introduction

The University of Limerick, together with the University of Rostock, have developed a novel, non-invasive, optical device for the continuous measurement of both haemoglobin and stroke volume. The measurement of stroke volume could then theoretically be used to predict fluid responsiveness. The device relies upon the basic principles of photoplethysmography described in the previous chapter. Although it has been tested in laboratory conditions and with small numbers of patients, it has yet to be validated clinically and exists only in a prototype form. Data regarding sensitivity, accuracy or precision of the device have not been published by the developers and are not otherwise available.

2.2.Description of the device

The same device was used throughout each of the studies described in this work. The measurement part of the device consists of a probe which fits over the finger, similar to commercially available pulse oximeters. The probe contains three light emitting diodes (LEDs) on the dorsal aspect of the finger, and light from these is detected by a photodiode receiver on the palmer aspect of the finger. Information from the probe is sent to a box (approximately 17 x 10 x 3 cm in dimension) close to the probe. This box contains a MSP430 microcontroller (Texas Instruments, Dallas, TX, USA) which carries out both time-based control of the LEDs/receiver and all signal processing. The purpose of maintaining a short distance between the probe and the box is to minimise electrical interference to the signals as they pass between each, which can be a source of error. The data generated from the signal processing is then sent to a medical-grade computer via a Universal Serial Bus (USB) cable, and analysed using LabVIEW software (National Instruments, Austin, TX, USA).

2.3.Haemoglobin measurement

The three LEDs in the probe emit light at specific wavelengths: 670, 810 and 1300 nm. 810 nm was chosen as it is very near an isobestic point where the absorption coefficients of oxyhaemoglobin and deoxyhaemoglobin are identical and therefore their measurement is independent of arterial oxygen saturation[1]. Pure water does not absorb much light in the visible spectrum (approximately 380 to 740 nm), but absorption increases from about 900 nm upwards. The developers of the device chose to measure this absorbance at 1300 nm as a convenient way to adjust haemoglobin measurements for variations in water content[1, 2]. The 670 nm wavelength is used in the calculation of arterial oxygen saturation only and is not a feature of Hb measurement. A standard silicon photodiode, as is normally found in pulse oximeters, would only be capable of measuring the absorption coefficients at 670 and 810 nm, so an indium-gallium-arsenide photodiode[3] is instead used to measure at all three wavelengths as it has a spectral range of 400-1700 nm. Assumptions are made that red blood cells consist mostly of water, and that plasma mostly contains water. Of course, these assumptions over-simplify the situation, and are potential sources of error. The software calculates the "ratio of ratios" of absorbances at 810 and 1300 nm in the varying and non-varying components of the PPG waveform, and this number can then be transformed to display the Hb

using the device's calibration curves. The Hb displayed on the screen represents a 50-point moving average.

In an initial study, the developers of the device examined the absorbances of artificially varying haemoglobin concentration in a closed cardiopulmonary bypass circuit (using donor blood, and with no patient involved). Over a range of haemoglobin concentrations of 50-206 $g.l^{-1}$, and partial least squares regression calibration, they found the device to be accurate[1]. They carried out further calibration using just 27 volunteers, whose haemoglobin concentrations were also measured using a HemoCue (HemoCue, Ängelholm, Sweden), and the resulting calibration curves were validated using 15 more volunteers. There is no information as to the range of haemoglobin concentration among the initial 27 subjects. Reading from the published Bland-Altman plot relating to the validation exercise with the subsequent 15 volunteers, the range among the volunteers appears to have been 117.6-166 $g.l^{-1}$, which falls broadly in the normal range. Two major flaws with this study were that the initial measurements were taken from pulseless flow, which may lead to errors of calculation of absorption as there is then no varying part of the PPG signal, and that the donated blood used in the flow circuit contained no "plasma, proteins, leukocytes or thrombocytes".

2.4. Stroke volume measurement

For measurement of stroke volume, the 810 nm wavelength is used to plot the PPG waveform. The area under the varying part of the resulting curve is calculated using integration (an adaptive variant of the Gauss-Lobatto quadrature[4]). The developers term this area 'stroke volume' (SV) although strictly speaking this is not correct. From this they calculate stroke volume variation (SVV) as:

$$SVV\ (\%) = (SV_{max} - SV_{min}) / SV_{mean}$$

where SVmax and SVmin are the maximal and minimal values of SV respectively over a complete respiratory cycle. SVmean is the mean of all measurements of SV across the same respiratory cycle[5]. Rising velocity (RV) is also calculated as the ratio of the maximal amplitude of systole over its duration. It is not made clear as to how these values are then used to arrive at a single calculation. Values are calculated every cardiac cycle and a mean value is displayed every six seconds. This mean represents a 25-point moving average. In these initial studies, the device required initial calibration in each patient, using another method of measurement for cardiac output or stroke volume. For the purposes of our study, only the raw output of the device was considered for statistical analysis to attempt to establish correlation.

In the first report of monitoring patients using this function of the device, patients from intensive care units undergoing monitoring using either transpulmonary thermodilution via a pulmonary artery catheter (PAC), or the less invasive PiCCO system (Pulsion Ltd, Munich, Germany) had their stroke volumes compared to the output from the new device. They do not specify how many patients were studied or how many patients had PAC versus PiCCO monitoring, nor do they publish any demographic data relating to these patients. No attempt at summarising the results is made. It is difficult to draw any conclusions from this paper, other than from one graph representing an "unstable" patient where the device suggested the patient required treatment with a bolus of intravenous fluid (as a greater than 20% drop in SV over 22 minutes was evident), whilst at the same moment PiCCO demonstrated that SV had in fact fallen by just 5.2%, and would not therefore require intervention[6].

Of note, in this and a further study[5] there was no distinction made between ventilated and non-ventilated patients which would be expected to have a dramatic change on results, as it is well known that positive pressure ventilation is required to induce useful and measurable variation in the PPG waveform (see section 1.9, Pulse oximetry plethysmographic variation and Plethysmographic Variability Index as monitors of fluid responsiveness).

2.5.Differences between the novel device and similar available devices

As described in the introduction, there are two other devices already commercially available which can measure haemoglobin non-invasively.

Masimo Corporation's (Irvine, California, USA) two devices, the Radical-7 and the Pronto-7 consists of a finger clip type probe with light emitting diodes and photodiode receivers. Single-use probes for use on various sites (fingers, toes) are available, along with an ear probe. The details of wavelengths, materials and algorithms used are not available. Unlike the novel device, the probes connect directly to a proprietary display via a non-universal cable. Apart from haemoglobin, the device can also measure carboxyhaemoglobin, methaemoglobin, oxygen saturation and measurements Masimo terms "oxygen content" and "acoustic respiratory rate". The Radical-7's display is designed for continuous monitoring purposes, such as during anaesthesia, while the Pronto-7 is smaller and designed to be portable for use on a ward or in clinics. The basic technology in each is otherwise similar.

The manufacturers publish minimal information regarding error rate and performance in hypoperfusion states. There are a small number of studies investigating the device's performance in hypoperfusion states.

Two studies found that the Radical-7 performed well as an oximeter in low perfusion states but did not specifically test the haemoglobinometry function[6, 7]. A further two studies found good performance of haemoglobinometry at low perfusion states[8, 9], but one study found that the correlation between the Masimo device and a laboratory test for haemoglobin was best in patients with a normal perfusion state and so may not perform as well in a lower perfusion state[10].

Regarding the novel device, no information regarding error rate, performance in hypoperfusion states or data pairing in non-critically low haemoglobin states was known prior to the commencement of the studies included in this thesis.

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3.Study 1 - Clinical evaluation of a novel technology for non-invasive and continuous measurement of plasma haemoglobin concentration

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3.1.Abstract

Background

Measuring haemoglobin usually requires sampling and processing of blood. In this study, we undertook the first clinical evaluation of a novel, non-invasive device for the continuous measurement of plasma haemoglobin concentration.

Methods

We enrolled twenty five patients undergoing elective cardiac surgery. At four pre-determined intervals, samples of blood were taken for plasma haemoglobin estimation on a blood gas analyser and a laboratory device and were compared with the plasma haemoglobin estimation on the novel device using the Bland-Altman method.

Results

The 95% limits of agreement for estimation of plasma haemoglobin in the cases of the device versus laboratory, the device versus the blood gas analyser and the blood gas analyser versus the laboratory were 101.3 $g.l^{-1}$, 103.1 $g.l^{-1}$ and 14.5 $g.l^{-1}$ respectively. The bias (mean difference) in each case was 27.4 $g.l^{-1}$, 25.1 $g.l^{-1}$ and 2.4 $g.l^{-1}$ respectively.

Conclusions

We conclude that the novel device in its current form is not a suitable replacement for more invasive methods of determining plasma haemoglobin in patients in the setting of cardiac surgery. However, lessons learned from the study will help to improve the device's future performance.

3.2.Introduction

In many clinical situations (such as during cardiac, vascular surgery or following trauma), plasma haemoglobin concentration is measured frequently and/or urgently. Currently, this requires sampling and processing of blood, either with a formal laboratory full blood count, with a blood gas analyser, or with a point-of-care device. A continuous, non-invasive and accurate method would allow for more rapid decision making in such situations.

The Optical Fibre Sensor Research Centre at the University of Limerick together with the Institute of General Electrical Engineering at the University of Rostock, Germany have co-developed a novel device for the non-invasive, optical, real-time measurement of haemoglobin, which calculates a ratio of the absorbances of different wavelengths of light passed through a fingertip to estimate haemoglobin, in a similar manner to a standard pulse oximeter[1]. Masimo Corporation has previously gained FDA approval for a non-invasive pulse haemoglobinometer (the Radical-7 pulse CO-oximeter) and several studies have evaluated its accuracy[2-6]. This device uses multiple wavelengths of light to determine haemoglobin, (although the wavelengths employed have not been published). The device which is the subject of this investigation utilises just two wavelengths of light which would lower the cost of production,

and much of the signal processing takes place within the finger probe itself to minimise interference. Differences and similarities between the novel device and the Radical-7 are listed in Table 1.

During cardiopulmonary bypass, patients can undergo large and rapid changes in haemoglobin secondary to blood loss, fluid administration, or blood product transfusion. In addition, the institution of cardiopulmonary bypass results in haemodilution, and accordingly these cases present an ideal opportunity to study a wider range of haemoglobin within the population group. The primary objective of this study was to compare haemoglobin estimation using the novel device with a standard laboratory device (XE-2100, Sysmex Corporation, Kobe, Japan). The secondary objectives were to compare results from the novel device with a blood gas analyser (GEM Premier 4000, Instrumentation Laboratory, Bedford, MA, USA) and finally to compare results from the standard laboratory device with those from the blood gas analyser.

3.3.Methods

With institutional ethical committee approval (Clinical Research Ethics Committee of the Cork Teaching Hospitals, 21/10/2010) and having obtained written informed consent from each, 25 American Society of Anesthesiology (ASA) grade III patients scheduled for elective cardiac surgery requiring cardiopulmonary bypass were studied. Exclusion criteria were the presence of any known haemoglobinopathy or recent dye or contrast studies as these may interfere with the measurement of haemoglobin, or the intra-operative use of an intra-aortic balloon pump as this would significantly alter the contour of the plethysmographic waveform and prevent correct functioning of the device.

Each patient's age, gender, height, weight, body mass index, baseline haemoglobin and temperature (via a nasal temperature probe) were recorded. In addition, each patient's smoking history was recorded. Following induction of anaesthesia, the novel device was fitted on the index finger of each patient's right hand (unless the right radial artery was to be used for grafting, in which case the left index finger was used). Blood was drawn from the arterial catheter via the port closest to the patient at four standard time points using the following technique. Initially 10 ml blood/heparinised saline was drawn from the arterial catheter. Subsequently 6 ml of arterial blood was drawn (in a second

syringe) and 4.1 ml of this blood was transferred to a standard Lithium-Heparin blood sample bottle and sent to the haematology laboratory for haemoglobin estimation using the hospital's standard CO-oximeter (XE-2100, Sysmex Corporation, Kobe, Japan) for analysis. The remaining blood from this syringe was then transferred to an arterial blood gas syringe, and processed using the GEM Premier 4000 blood gas analyser. The original 10 ml of blood/heparinised saline was then returned to the patient to minimise unnecessary blood loss. To determine haemoglobin, the device first calculated a coefficient from the measured absorbances of two wavelengths of light through the varying part of the pulse signal, similar to the method used in standard clinical pulse oximeters. The device then referred this coefficient to a lookup table and displayed the result on-screen as haemoglobin. This initial haemoglobin determination served as an additional calibration for further measurements within the same patient. At each time point, the patient's haemoglobin as displayed by the novel device was recorded, and an on-screen button was pressed which recorded the 50-point moving average of the haemoglobin coefficient at that time (i.e. the average of the most recently acquired 50 haemoglobin coefficients). The four time points selected were, (i) skin incision, (ii) two minutes after completion of administration of the first dose of heparin (pre-bypass), (iii) two minutes after completion of the first dose of protamine (post-bypass) and (iv) at completion of the final skin suture (at the end of surgery). We chose a study sample size (25 subjects)

arbitrarily to generate 100 paired samples across the four time points for each comparison. Scatter plots were constructed and a line of equality was included on each plot for the each following comparisons (i) device haemoglobin vs. full blood count haemoglobin (the primary outcome), (ii) device haemoglobin vs. blood gas analyser haemoglobin and (iii) blood gas analyser haemoglobin vs. full blood count haemoglobin. The laboratory device was considered the 'gold standard' for comparing the methods of measurement. The blood gas analyser was selected for comparison on the basis that anaesthetists commonly utilise this device to measure haemoglobin intraoperatively as a time-saving measure rather than sending a sample to the laboratory. The final comparison, between the blood gas analyser and the laboratory device was carried out as previously the limits of agreement between these have been found to be quite wide[7]. Stata Statistical Software: Release 13 (StataCorp LP, College Station, TX, USA) was used for these, and also to construct Bland-Altman[8] plots for each comparison. The method proposed by Bland and Altman[9] for the calculation of bias and limits of agreement was applied using MedCalc (MedCalc Software, Ostend, Belgium), as this study required repeated measurements of haemoglobin within the same subjects in a situation where the true value of haemoglobin was varying. Statistical analysis included descriptive statistics and tests of equality of variances across the range of patient means (Spearman's Rho), an assumption required for Bland-Altman analyses.

3.4. Results

Twenty-five patients were enrolled in the study. Patient characteristics, baseline haemoglobin and the planned surgical procedure are summarised in Table 2. On two occasions during the study, no samples were recorded across all three modalities due to observer omission. Of the remaining 98 sets, one sample processed with the blood gas analyser was not recorded, again due to observer omission. Two further laboratory full blood count samples were not recorded due to breaches of protocol (one was not taken, the other not processed) leaving 95 complete sets of paired data for analysis.

Fifteen patients had never smoked and one patient was an active smoker of 84 pack years. Nine patients were former smokers whose cessation dates ranged from six weeks to 61 years prior to surgery. The active and former smokers had a mean of 28.3 pack years. In the early part of the study period we encountered six instances (in the first seven participants) of “freezing” of the on-screen display of haemoglobin, requiring a system reboot between sample points. The problem was found to be due to a software bug, which was corrected by the developers before enrolment of the eighth participant; the problem recurred on only one further occasion (the last participant).

The assumption that the within-subject variance was the same for all subjects was reasonable, as low values of Spearman's Rho showed that there was no evidence of a relationship between variability of the differences and the average of the two measurements. The results of the Bland-Altman analysis including the mean differences, 95% limits of agreement and Spearman's Rank Order correlation values for each comparison are summarised in Table 3. Bland-Altman plots and scatter plots are shown in Figure 1.

3.5.Discussion

Our results show that, in its current form the novel device studied is not a suitable replacement for invasive methods of determining haemoglobin in patients in the setting of cardiac surgery. The 95% limits of agreement in the cases of the device versus the laboratory full blood count and the device versus the blood gas analyser demonstrate a very broad range in the reference interval (101.3 and 103 $g.l^{-1}$ respectively), which would be clinically unacceptable. The 95% limits of agreement for the blood gas analyser versus full blood count show a much closer agreement (a range of 14.5 $g.l^{-1}$) and a far lesser mean difference, indicating that these two methods are likely to be interchangeable. Graphs of haemoglobin measured by the novel device versus those measured by the laboratory full blood count and the blood gas analyser show a large scatter about the line of equality in comparison with the blood gas analyser versus full blood count (Figure 1). We did not compare the novel device with other non-invasive haemoglobin measurement devices such as Masimo's Radical-7 as the novel device has not yet been clinically validated or compared to a gold standard.

Previous studies of non-invasive haemoglobin monitors have reported varying degrees of agreement with traditional methods. In their study analysing 335 paired measurements comprising 20 healthy volunteers

who underwent haemodilution (i.e. where the true haemoglobin value varied), Macknet et al[2] found a non-invasive pulse haemoglobinometer (Masimo Radical-7, Masimo Corporation, Irvine, CA, USA) and their reference method to have a mean difference of -1.5 $g.l^{-1}$ and that the difference between methods was <20 $g.l^{-1}$ for 97% of the measurements. Dewhirst et al[3] using Masimo's Radical-7 and a point-of-care analyser in children found the mean difference to be 1 $g.l^{-1}$ and that 80% of sample sets were within 20 $g.l^{-1}$. They concluded that the non-invasive device was valuable as a continuous trend monitor, but unacceptable to base transfusion decisions upon. This was a similar conclusion to that of Park et al[4] in their study of the Radical-7 in children undergoing neurosurgery. However, Nguyen et al[5] noted a poor correlation between the Radical-7 and laboratory full blood count in 41 patients following cardiac surgery and, in particular, noted that the difference between sampling methods varied considerably in repeated samples from the same patient at the same time (between -63 and +12 $g.l^{-1}$ for one patient). Together these findings show that this method of non-invasive measurement of haemoglobin has some promise but is, as yet, unsuitable for use in the clinical setting of cardiac surgery.

The close level of agreement between the GEM Premier 4000 blood gas analyser and the laboratory full blood count has not been shown before and is clinically relevant as many cardiac surgical centres now rely on

similar analysers for the rapid assessment of haemoglobin. An alternative point-of-care device has previously been shown to be a valid method in the setting of critical care[10].

There are several potential sources of error with this device that might explain the poor level of agreement with more established methods for measuring haemoglobin. First, the data used to calibrate the device were obtained from a relatively small (n=27) sample of healthy volunteers which were compared to the HemoCue (HemoCue, Ängelholm, Sweden) device[1]. Due to the small sample size, any the effect of any error with readings would be greatly amplified. Also, the HemoCue is a portable point-of-care device which could not be considered a 'gold standard'. Second, as subsequent within-patient estimations of haemoglobin relied in part on the initial reading, drift is likely to have occurred leading to increasingly inaccurate estimations. During bypass (between time points two and three in each case), the device would have lost all data acquisition due to the lack of a pulsatile signal, which may have exaggerated any drift present. Third, the patient group studied presented specific challenges that potentially lead to problems with signal acquisition. (i) Patients undergoing cardiac surgery are more likely to have lower perfusion states than healthier patients. (ii) Patients with moderate and severe congestive heart failure have increased stiffness and decreased compliance of the brachial arteries[11]. (iii) Hypothermia

alters vasomotor tone, which is of particular concern in patients following cessation of cardiopulmonary bypass. (iv) Cardiopulmonary bypass itself elicits an inflammatory response, which can lead to alterations in vasomotor tone. A further analysis of our data showed that the mean difference of the device haemoglobin and the full blood count haemoglobin before cardiopulmonary bypass was 17.4 $g.l^{-1}$, while the mean difference was 37.4 $g.l^{-1}$ following cardiopulmonary bypass. This is likely due to a combination of drift as described, inflammatory effects of cardiopulmonary bypass, patient hypothermia following bypass and the use of vasoactive agents (which were not recorded as part of this study). Fourth, the presence of carboxyhaemoglobin and methaemoglobin may lead to inaccuracies in the estimation of haemoglobin. This is a potential confounder with any estimation of haemoglobin where carboxyhaemoglobin and methaemoglobin concentrations are not measured and then subtracted from the estimated haemoglobin. Our study was not designed to take this into account. Fifth, following completion of the study, the continuously recorded data from the novel device were analysed to retrieve the haemoglobin coefficient at each sample point. It was discovered that on 52 of the 100 data points the signal detected by the novel device was of such a poor quality that measurements could not be obtained and therefore the haemoglobin coefficient could not be determined. This led us to conclude that the haemoglobin calculated by the device for each of these time points is

likely to be inaccurate. Despite this, when these data points were excluded, the mean difference of the device haemoglobin and the full blood count haemoglobin was actually worse at 29.2 $g.l^{-1}$. Sixth, the software issues that lead to the device freezing in the earlier part of the study, as previously mentioned, may have further contributed to the loss of calibration in the subsequent samples in the affected patients.

Improvements could be made to the signal processing algorithms within the device, which might lead to less error in lower perfusion states or with changes in vasomotor tone. Calibrating the device empirically using a far larger group of volunteers, such as the thousands of volunteers used to calibrate standard commercial pulse oximeters would likely increase the accuracy of this device. Revision of the software to ensure that further freezing does not occur during device operation could also prevent intra-patient calibration problems. Results could also be improved using the simple method proposed by Miyashita et al whereby the difference between the haemoglobin reading from the device and a laboratory or point-of-care value is used to adjust subsequent readings on the device (within the same patient)[12]. This method improved the accuracy of non-invasive haemoglobin measurement in 17 patients (with 71 measurements), but only included those undergoing abdominal surgery. Of course, the device could not then be truly described as 'non-invasive'.

There are limitations to our study. First, the precision of our gold standard was not established at each sample point. This would have required as much as three times the volume of blood to be withdrawn from each patient at each time point, which we deemed unacceptable. Second, the acceptable 95% limits of agreement were not stated a priori, although the calculated limits of agreement were so wide as to make clear that the device would not be clinically useful at this point. Finally, the investigators were not blinded to the output from the device or the results from the blood gas analyser.

Finally, details of each participant's smoking history were recorded as at the time of design of the study's protocol it was thought that the presence of carboxyhaemoglobin may have prove to be a source of interference to the measurement of haemoglobin. However, no research has been published to date which indicates that this may be the case.

Our results indicate that, in its current form, the novel device studied is not suitable for clinical use; several technical challenges (outlined above) will need to be addressed before it could be recommended for clinical use.

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Competing Interests

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A. J. Broderick was awarded the College of Anaesthetists of Ireland's Annual Research Award in March 2011 for this project. The University of Limerick has applied for patents in respect of the novel device for non-invasive haemoglobin estimation. None of the authors hold any patents in relation to the device.

3.6. Tables

Table 1. Similarities and differences between the novel device and the Radical-7 (Masimo Corporation).

Novel Device	Radical-7
Measures O_2 saturations and Hb only	Measures heart rate, O_2 saturations, Hb, COHb, MetHb, Pleth Variability Index
Clip-type finger probe only	Clip-type probe which can be used on fingers or toes, ear probe also available
2 wavelengths (810 and 1300 nm)	Multiple wavelengths (details not published)
Signal processing close to the probe	Signal processing in the display unit
Display unit not compatible with existing intraoperative monitoring systems	Display unit compatible with a range of intraoperative monitoring systems
Calibrated using 27 volunteers	Calibration data unavailable

Table 2. Summary of patients' characteristics and type of surgery. Values are number, median (IQR [range]) or number (proportion).

Number of subjects	25
Age; years	67 (57-74 [34-80])
Sex; M: F	9 : 16
Height; cm	165 (160-172 [152-184])
Weight; kg	80 (68-90 [51-147])
Body mass index; $kg.m^{-2}$	27.9 (24.1-31.3 [20.6-56.9])
Baseline [Hb]; $g.l^{-1}$	133 (124-146 [110-163])
Baseline temperature; °C	36.2 (36-36.5 [36-37])
CABG	12 (48%)
Valvular surgery	9 (36%)
Combined (CABG and valvular) surgery	3 (12%)
Atrial myxoma	1 (4%)

IQR=Interquartile range

[Hb]=plasma haemoglobin concentration

CABG=Coronary artery bypass graft

Table 3. Comparison between the three study methods of plasma haemoglobin estimation. Values are mean [upper, lower 95% limits of agreement] and number (significance level).

Method Comparison	Device vs FBC	Device vs BGA	BGA vs FBC
[Hb] Mean Difference (bias); $g.l^{-1}$	27.4 [-23.2, 78.1]	25.1 [-26.5, 76.6]	2.4 [-4.8, 9.7]
Spearman's Rho†	-0.01 (0.97)	0.02 (0.92)	-0.05 (0.81)

[Hb]=plasma haemoglobin concentration

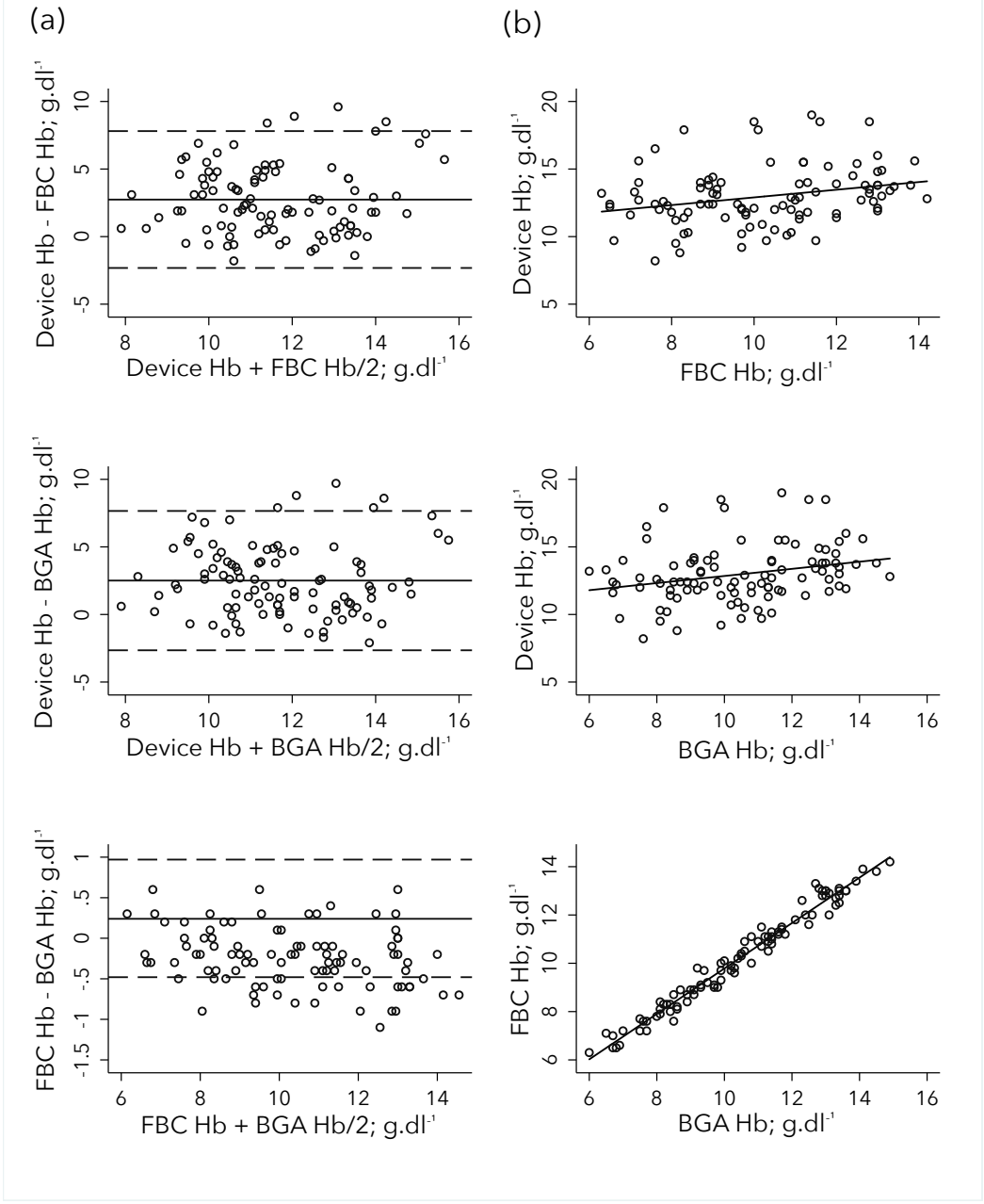
FBC=full blood count

BGA=blood gas analyser

†Calculation is based on standard deviation of differences between two methods vs. average of two methods per subject

3.7. Figures

Figure 1 (following page). (a) Bland-Altman plots and (b) scatter plots for the comparisons between each method of plasma haemoglobin (Hb) estimation: the novel device, laboratory full blood count (FBC) and the blood gas analyser (BGA). The solid horizontal line in each Bland-Altman plot indicates the mean difference (bias) between methods; the broken lines indicate the 95% limits of agreement.


(a)
(b)
Device Hb - FBC Hb; g.dl-1
Device Hb + FBC Hb/2; g.dl-1
Device Hb; g.dl-1
FBC Hb; g.dl-1
Device Hb - BGA Hb; g.dl-1
Device Hb + BGA Hb/2; g.dl-1
Device Hb; g.dl-1
BGA Hb; g.dl-1
FBC Hb - BGA Hb; g.dl-1
FBC Hb + BGA Hb/2; g.dl-1
FBC Hb; g.dl-1
BGA Hb; g.dl-1

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4.Study 2 - Clinical evaluation of a novel device for the non-invasive measurement of haemoglobin in the obstetric population

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4.1.Abstract

Background

Appropriate diagnosis and treatment of anaemia in pregnant women usually requires sampling and processing of blood. Accurate and non-invasive measurement of haemoglobin would make this much easier and potentially lead to cost-savings with improved outcomes. In this study we compared haemoglobin measurement using a non-invasive novel device with a laboratory standard.

Methods

We compared the routinely measured haemoglobin from one hundred women attending their twenty-week antenatal check with that of the novel device using scatter and Bland-Altman plots.

Results

The mean difference of haemoglobin concentration between the methods was 10.4 $g.l^{-1}$, with a standard deviation of 19.8 $g.l^{-1}$. The 95% limits of agreement were -28.4 to 49.1 $g.l^{-1}$. The coefficient of determination (r^2) between the two methods was 0.00018769. A measurement error occurred whereby the device was not reset correctly between measurements which may have lead to inaccurate results.

Conclusions

The novel device is not an acceptable method of haemoglobin concentration measurement in pregnant women at present. We document possible refinements which may lead to greater accuracy in this novel device in future studies. The measurement error means that our results should be interpreted with caution.

4.2.Introduction

Plasma haemoglobin concentration is a frequently performed blood test in all areas of healthcare. This usually requires venepuncture (with inherent discomfort), sampling and processing of blood, either in the laboratory as a formal Full Blood Count (FBC), or with a point-of-care analyser. In the case of a laboratory FBC, an urgently required result may not be obtainable by the clinician in a timely manner. A reliable, non-invasive, point-of-care device would allow for painless and rapid haemoglobin estimation, while potentially decreasing the cost of processing blood samples. Such a device would be useful in clinical circumstances where haemoglobin concentrations are rapidly changing or need to be monitored closely, such as pregnancy, trauma, or cardiac surgery.

The World Health Organization reports that 18% of pregnant women from industrialised countries have iron-deficiency anaemia[1], and consequently pregnant patients attending antenatal clinics frequently undergo blood sampling for haemoglobin estimation. At present, all pregnant women booked into Cork University Maternity Hospital have a FBC taken at the 20-week antenatal check. Most of these women also have a FBC taken by their general practitioner prior to booking, and all those considered to be at risk of anaemia will have subsequent frequent

blood sampling. Earlier and more frequent measurement of haemoglobin may allow for more timely iron supplementation, as well as the ongoing measurement of efficacy of treatment in those found to require iron supplementation.

Recently, photoplethysmography (PPG) has been used for the non-invasive measurement of haemoglobin concentration, in a similar manner to pulse oximetry. Masimo Corporation (Irvine, CA, USA) currently produce two devices utilising this technology; Radical-7™ and Pronto-7™. These devices have been tested clinically and were the subject of a recent systematic review and meta-analysis[2]. Masimo's devices use seven wavelengths of light, the precise values of which are protected under patent. Another device, manufactured by OrSense (Nes Ziona, Israel), the NBM-200™, uses occlusion PPG to provide an intermittent estimation of haemoglobin concentration. The Optical Fibre Sensor Research Centre at the University of Limerick together with the Institute of General Electrical Engineering at the University of Rostock, Germany have co-developed a different novel device for the non-invasive, optical, real-time measurement of haemoglobin, which also makes use of PPG[3]. In contrast to Masimo's device, the novel device uses just two wavelengths of infrared light/near-infrared light, which has a potential cost saving. This device has also been shown to accurately measure very low haemoglobin concentrations in-vitro (38.7 $g.l^{-1}$)[4]. An

initial investigation of the device (in the setting of cardiac surgery with multiple within-subject sampling) demonstrated poor correlation with laboratory FBCs and a blood-gas analyser, particularly in the period following cessation of cardiopulmonary bypass. This was due to several factors, many of which were unique to that setting[5]. However, the device has not been tested in the setting of single patient samples at an antenatal clinic until now. There was no opportunity to make improvements to the device, as this study and the previous one ran simultaneously. The similarities and differences between these three devices are summarised in Table 1.

The primary objective of this study was to compare Hb estimation using the novel device with standard laboratory measurement (XE-2100 Sysmex Corp., Kobe, Japan), in pregnant patients presenting for their 20-week antenatal check.

4.3.Methods

With institutional ethical committee approval (Clinical Research Ethics Committee of the Cork Teaching Hospitals, 30/05/2011) and having obtained written consent from each, 100 adult females attending the antenatal clinic of Cork University Maternity Hospital for their 20 weeks' gestation check who were due for routine FBC were enrolled in this prospective observational study. It is routine practice at this institution to recommend all women undergo a FBC at this stage of gestation. Exclusion criteria were the presence of any known haemoglobinopathy, recent dye or contrast studies, or the presence of acrylic nail polish/ coverings, all of which would potentially interfere with the absorption of light from the device.

Each participant's age, height, weight, body mass index (BMI) and smoking status (with smoking history as appropriate) were recorded. The novel device was placed on the index finger of the opposite upper limb to that used for blood sampling. This avoided any interference from the tourniquet with light absorption by the device. In each case the device was left in place for one minute to allow its reading to stabilise. As a venous blood sample was drawn, the haemoglobin concentration measured by the device was recorded. The blood sample was sent to the hospital's haematology laboratory for analysis using the hospital's CO-

Oximeter (XE-2100, Sysmex Corporation, Kobe, Japan) and this measurement of haemoglobin concentration was subsequently recorded. The investigators were blinded to the results of the laboratory FBCs until after the final participant had been enrolled and recorded.

To determine plasma haemoglobin concentration, the device first calculates a coefficient from the measured absorbances of two wavelengths of light through the varying part of the pulse signal, similar to the method used in standard clinical pulse oximeters. The device then refers this coefficient to a reference table and displays the result on-screen as haemoglobin concentration. This initial haemoglobin determination serves as a further calibration for further measurements within the same patient. At the time of sampling, the patient's haemoglobin as displayed by the novel device was recorded, and an on-screen button was clicked which recorded the 50-point moving average of the haemoglobin coefficient at that time (i.e. the average of the most recently acquired 50 haemoglobin coefficients). All data were recorded on case record forms and subsequently entered into an Excel spreadsheet (Microsoft, Redmond, WA, USA). A scatterplot comparing novel device haemoglobin concentration and laboratory haemoglobin concentration was constructed, and a line of equality added. The coefficient of determination (r^2) was calculated for the comparison, and a Bland-Altman[6] plot of the mean versus the difference in haemoglobin

concentration for each pair was produced. Stata Statistical Software: Release 13 (StataCorp LP, College Station, TX, USA) was used to produce these plots.

4.4. Results

100 patients were enrolled in the study. Patient characteristics are summarised in Table 2. In one case, the height and weight were not recorded, although the patient's BMI was. Median haemoglobin concentration was 117 $g.l^{-1}$. Participant's smoking status is summarised in Table 3. Of the active smokers, the mean number of cigarettes per day smoked was 6 (range 2 to 10). Of those who had previously smoked, the mean time since cessation was 4.12 years (range 0.29 to 16) and the mean number of cigarettes per day smoked was 8.71 (range 1 to 20).

A scatter plot with line of regression and a Bland-Altman plot are shown in Figures 1 and 2 respectively. The coefficient of determination (r^2) between the two methods was 0.00018769. The mean difference (bias) of haemoglobin concentration between the methods was 10.4 $g.l^{-1}$, with a standard deviation of the bias (accuracy) of 19.8 $g.l^{-1}$. The 95% limits of agreement (calculated as the bias ± 2 standard deviations) were -28.4 to 49.1 $g.l^{-1}$.

4.5. Discussion

Our results show that the novel device is not currently suitable as a replacement for more invasive methods of haemoglobin concentration estimation in the setting of antenatal patients of approximately 20 weeks' gestation. The poor correlation and broad range of the 95% limits of agreement (up to 77.5 $g.l^{-1}$) would not be clinically useful in the diagnosis and management of maternal anaemia.

Few studies have investigated the use of non-invasive haemoglobin concentration estimation in the pregnant population. Butwick et al compared Masimo's Radical-7 with laboratory measurements in patients before and after caesarean section delivery and found a significant positive bias at baseline (12.2 $g.l^{-1}$) and broad limits of agreement (-9 to 33.3 $g.l^{-1}$) concluding that the device was not useful for clinical purposes in this setting[7]. This was confirmed in a similar study by Skelton et al which found the overall limits of agreement for the Radical-7 were -42 to 20.2 $g.l^{-1}$ and that it gave lower and less accurate readings than the HemoCue (HemoCue, Ängelholm, Sweden)[8]. An investigation of non-invasive haemoglobin monitoring in pregnant patients carried out using the NBM-200 (OrSense, Nes Ziona, Israel) found a bias of 1 $g.l^{-1}$ with narrower 95% limits of agreement (-15.9 to 17.9 $g.l^{-1}$) than our study[9]. Crowley et al investigated the use of Masimo's Rad-87 device to detect

anaemia in a population sample that included (but was not exclusive to) pregnant women. They did not report bias, precision or limits of agreement, but did note that the Pearson correlation coefficient was r=0.59 between the device and invasive haemoglobin concentration estimation, and found that the device had a 90% and 92% sensitivity in detecting true haemoglobin less than 120 and 130 $g.l^{-1}$ respectively[10]. Notwithstanding the results of these studies, we felt that there was equipoise as to whether the novel device would perform better than other devices due to its differing method of measurement (the NBM-200 being based on occlusion spectroscopy, and the Radical-7 using unknown wavelengths).

Our wide limits of agreement are consistent with these studies' findings. A recent systematic review and meta-analysis of non-invasive haemoglobin measurement devices concluded that limits of agreement were still quite broad despite a low bias, generally meaning that clinicians should exercise caution when using output from these devices to inform decisions regarding blood transfusion[2]. Of note, the authors of that review included only 6 of the 32 identified studies in their analysis, suggesting heterogeneity between studies and their protocols. Previously, Rice et al specifically reviewed the Radical 7 device and also concluded that published studies indicated that the device should not be used to determine the need for blood transfusion[11]. In our study, the bias

of 10.4 $g.l^{-1}$ indicated a tendency for the device to overestimate haemoglobin. The most significant example of this was a woman whose haemoglobin concentration was estimated as 111 $g.l^{-1}$ by the novel device, but whose formal laboratory measured haemoglobin concentration was only 75 $g.l^{-1}$. It is likely that the novel device would have failed to identify the severity of this patient's anaemia.

There are several reasons as to the poor level of agreement between the novel device and the laboratory FBC. First, it was discovered following completion of the study that the device had not been reset between each individual patient's haemoglobin measurement. As subsequent estimations of haemoglobin concentration (on subsequent patients) were self-calibrated against the initial reading, the reported value of haemoglobin would inevitably drift from the "true" value resulting in further inaccuracy. This was a major error in the conduct of the study and consequently all conclusions should be viewed with caution. Second, the device was calibrated using the data from a small sample of healthy volunteers (n=27)[3]. This narrow pool of probable homogenous data could lead to variations in estimating haemoglobin concentration from any measured haemoglobin coefficient. Third, our study was not designed to take into account the potential inaccuracies caused by the presence of carboxyhaemoglobin (COHb) and methaemoglobin. The smoking history of each participant was recorded, and indicated that

11% of participants were active smokers at the time of enrolment. However, as COHb levels were not measured, the knowledge that 11% of participants were active smokers can provide a guide only as the potential influence of COHb on the results. The bias for active smokers was 12.9 $g.l^{-1}$ with narrower limits of agreement (-14.2 to 40 $g.l^{-1}$) than for the study group as a whole, suggesting that the device performed marginally better in active smokers, although the sample size is too small to draw any conclusion. Finally, previous analysis of the plethysmographic pulse waveform in pregnant versus non-pregnant women found that the total power of pulse was lower in pregnant women, and particularly so in the second trimester[12]. The implications of this for our study are not clear, but it indicates plethysmographic differences between pregnant and non-pregnant subjects, which are not accounted for in the novel device.

Miyashita et al[13] have shown that simple refinements of the software algorithm can narrow the 95% limits of agreement of non-invasive haemoglobinometers. Masimo have introduced a similar modification to their devices (yet to receive FDA approval) which has also improved 95% limits of agreement[14]. It is reasonable to suggest that further refinements to the algorithms of the novel device will lead to more accurate haemoglobin concentration estimation. Improvements to filtering and

larger-scale calibration (with thousands of patients) could also be expected to improve the device's performance.

There are several limitations to our study. First, despite including 99 samples, this study is small and would require larger numbers to provide a more thorough clinical evaluation. Second, the novel device's estimation of haemoglobin concentration was not compared with the gold standard for haemoglobin measurement, the cyanmethaemoglobin method. Third, we did not define acceptable 95% limits of agreement a priori, although the actual limits of agreement were wide enough to indicate that the device is not currently acceptable for clinical use.

Although not a goal of this study, we found that 11% of participants in this study were active smokers at approximately 20 weeks' gestation. Although alarming considering the well-known harmful effects of antenatal smoking[15], this represents a lower incidence than that shown by a previous survey (in 2010) of maternal smoking patterns in Ireland, where the incidence was 23.5%[16]. A larger sample size would be required to establish a more accurate incidence, but may represent changing patterns in smoking in pregnant women in Ireland.

Our results show that the novel device is not an acceptable substitute for more established methods of haemoglobin concentration measurement

in pregnant women. Improved calibration using several thousand patients, together with refinements of the processing algorithms may lead to more accurate measurements of haemoglobin concentration with this novel device in future studies. The failure to reset the device correctly between measurements means that our conclusions should be viewed with caution.

Acknowledgements

This work was supported by the Science Foundation Ireland grant number: 11/RFP/ECE3335 and the Graduate Entry Medical School (GEMS), SRF fund, University of Limerick. Thanks also to Prof. Elfed Lewis of The Optical Fibre Research Institute, University of Limerick who manages the development the novel device. Sergi Andreuschenko (data processing) and Ulrich Timm (software and hardware) from the Institute of General Electrical Engineering at the University of Rostock, Germany contributed greatly to the device's development. Prof. Deirdre McGrath (Director of Education, Graduate Entry Medical School, University of Limerick) provides medical advice to the project. Sara Allen, Consultant Anaesthetist and Intensivist at Auckland City Hospital, Auckland, New Zealand advised on the preparation of this manuscript.

4.6. Tables

Table 1. Similarities and differences between the novel device, the Radical-7 (Masimo Corporation) and NBM-200 (OrSense).

Novel Device	Radical-7	NBM-200
Continuous readings	Continuous readings	Intermittent readings
Measures O_2 saturations and Hb only	Measures heart rate, O_2 saturations, Hb, COHb, MetHb, Pleth Variability Index	Measures heart rate, O2 saturations, and Hb
Clip-type finger probe only	Clip-type probe which can be used on fingers or toes, ear probe also available	Ring-shaped sensor which fits on a finger, a pneumatic cuff occludes blood supply transiently
2 wavelengths (810 and 1300 nm)	Multiple wavelengths (details not published)	No details regarding wavelengths
Signal processing close to the probe	Signal processing in the display unit	Signal processing in the display unit
Display unit not compatible with existing intraoperative monitoring systems	Display unit compatible with a range of intraoperative monitoring systems	No information on how compatible the display units is

Novel Device	Radical-7	NBM-200
Calibrated using 27 volunteers	Calibration data unavailable	Calibration data unavailable

Table 2. Summary of participants' characteristics. Values are number or median (IQR [range]).

Number of subjects	100
Height; cm	164 (161-168 [150-178])
Weight; kg	71.9 (62.95-80.25 [49-114.9])
BMI; $kg.m^{-2}$	25.9 (23.58-29.83 [19.8-39])
Haemoglobin; $g.l^{-1}$	117 (110.8-124 [75-140])

IQR=Interquartile Range

BMI=Body Mass Index

Table 3. Participants' smoking status

	N
Active	11
Previous	29
Never	60

4.7. Figures

Figure 1. A Bland-Altman plot for the comparison between plasma haemoglobin (Hb) estimation using the novel device and the laboratory full blood count (FBC). The solid horizontal line indicates the mean difference (bias) between methods; the broken lines indicate the 95% limits of agreement.

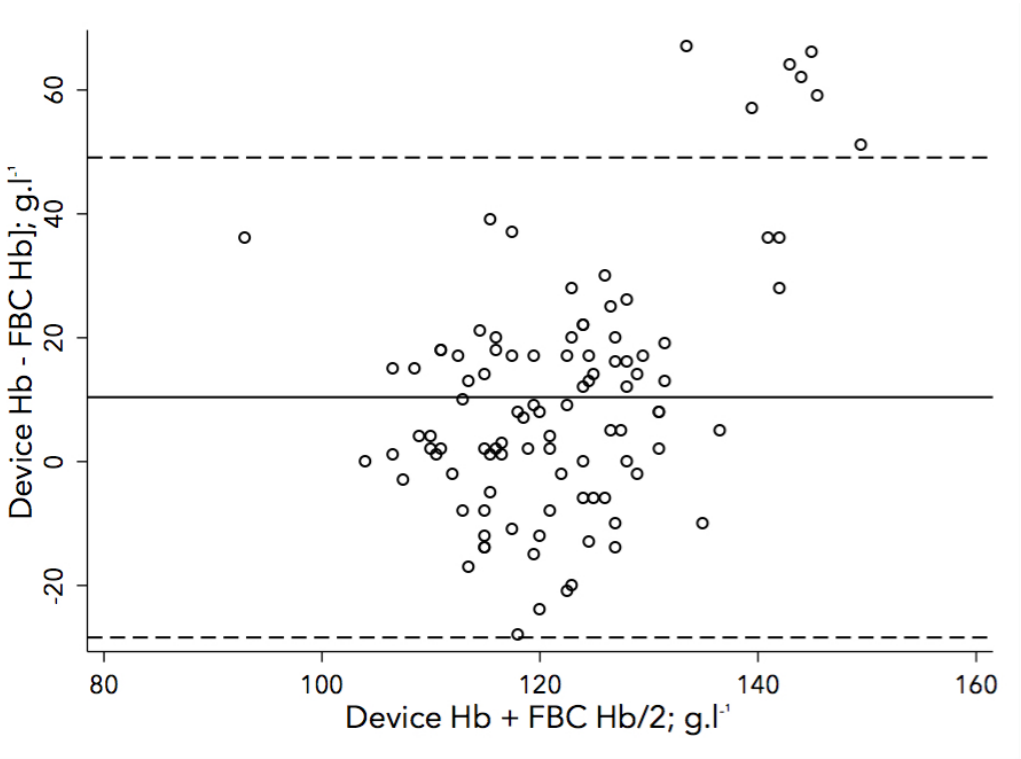
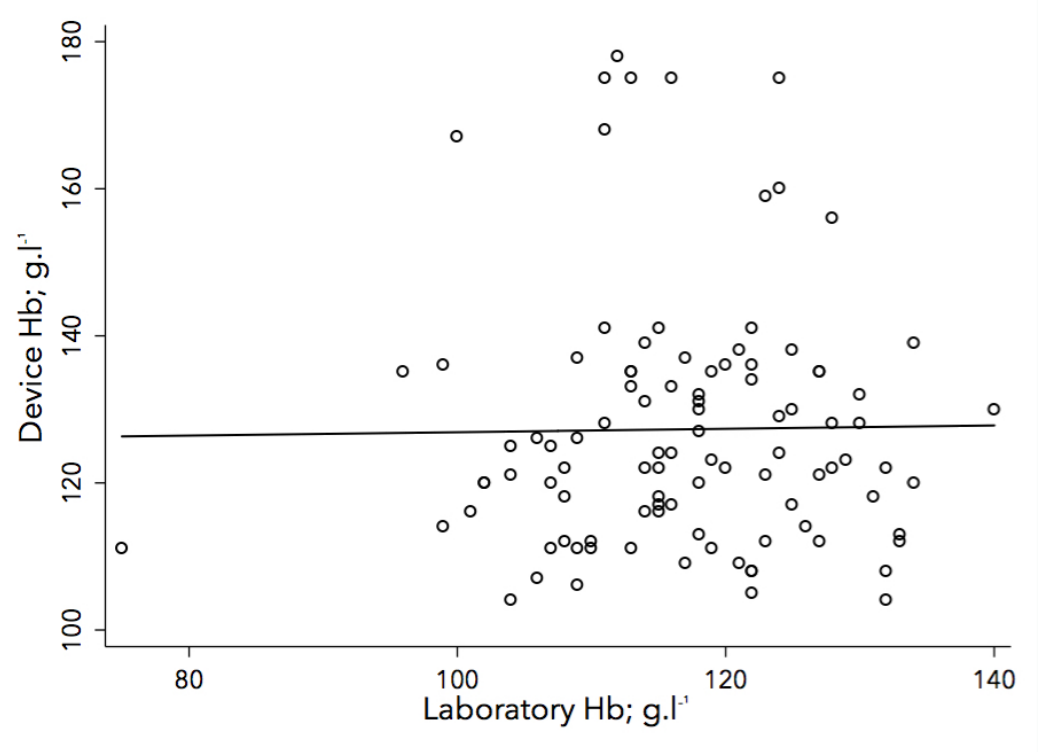


Figure 2. A scatter plot for the comparison between plasma haemoglobin (Hb) estimation using the novel device and the laboratory full blood count.



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5.Study 3 - Evaluation of a novel, non-invasive method for the estimation of stroke volume and the prediction of fluid responsiveness

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5.1.Abstract

Background

Cardiac output monitoring using a pulmonary artery catheter can estimate stroke volume, but is invasive and can lead to complications. Lesser invasive devices exist but none are truly non-invasive. We evaluated the ability of a prototype device both to measure stroke volume and to identify fluid responsiveness in patients undergoing cardiac surgery.

Methods

Twenty patients undergoing elective cardiac surgery with pulmonary artery pressure monitoring were enrolled. Measurements of stroke volume and cardiac output were made using the pulmonary artery catheter and the novel device before and after the administration of a fluid bolus. The two methods of measurement were compared using scatter plots. Fluid responders were retrospectively identified, and a receiver operating characteristic curve was plotted to evaluate the ability of the novel device to predict fluid responsiveness.

Results

The cardiac output and stroke volume as measured by the novel device correlated poorly with the pulmonary artery catheter, with an r^2 of 0.0145

and 0.0558 respectively. The area under the receiver operating characteristic curve for the prediction of fluid responsiveness by the novel device was 0.5844.

Conclusions

Our study shows that the novel device is not useful for the measurement of stroke volume or the prediction of responsiveness to a fluid bolus in this population.

5.2.Introduction

There is no gold standard for the clinical measurement of cardiac output and stroke volume, although the bolus thermodilution technique via pulmonary artery catheters (PACs) has been accepted as a "practical" gold standard since the 1970s[1]. However, this technique is associated with complications[2, 3] and has an inherent error of up to 20%[1]. The continuous thermodilution cardiac output (CCO) technique has been shown to agree clinically with the bolus thermodilution technique in several studies[4, 5]. Over the last number of years, various devices have been developed to allow measurement of cardiac output and stroke volume (PiCCO (Pulsion Ltd, Munich, Germany), LiDCO (LiDCO Ltd, London, England), Doppler oesophageal probes, partial CO_2 re-breathing, etc). Apart from bioimpedance methods such as NICOM (Cheetah Medical, Tel Aviv, Israel), none of these methods are truly non-invasive. Despite a promising early study demonstrating usefulness[6], NICOM (now marketed as "Starling SV") has been shown to not be reliable for estimating cardiac output or for predicting fluid responsiveness[7].

A rapidly responding, automated and truly non-invasive measurement of cardiac output, stroke volume or fluid responsiveness would avoid the

complications of more invasive methods, and could allow for easier goal-directed management of surgical patients.

It is known that the arterial pulse pressure variation (PPV), a system based on analysing the arterial pressure waveform, can reflect cardiac output and predict fluid responsiveness[8]. Indeed, dynamic indices such as PPV stroke volume variation (SVV) are now recommended for the measurement of fluid responsiveness[9].

Studies have shown that the information derived from the pulse oximetry plethysmograph (pulse oximetry plethysmograph variation or POPV) is as good as PPV for predicting fluid responsiveness[10] and is a reliable indicator of mild hypovolaemia in anaesthetised patients[11]. However, none of the POPV systems (which are no more invasive than a standard pulse oximetry probe) present automated data. However, there are no commercially available automated systems for calculating or monitoring POPV. In studies[11], the PPG waveform was printed out and the variation measured and calculated manually.

Masimo (Irvine, CA, USA) has developed a device, which measures the "pleth variability index" or PVI. PVI is a measure of the variation in the perfusion index (PI) which is calculated from the formula PI=(AC/DC) x 100, where AC is the varying portion of the light absorbance signal

caused by pulsatile blood flow, and DC is the constant portion of the light absorbance signal caused by skin, muscle, tendon, bone, and venous (non-pulsatile) blood[12]. Changes in PVI have been shown to reflect changes in POPV[12], and therefore have the potential to be used as a guide to fluid management of intraoperative patients[13].

The Optical Fibre Sensor Research Centre at the University of Limerick (UL) together with the Institute of General Electrical Engineering at the University of Rostock, Germany have co-developed a novel prototype research device that has the potential to non-invasively and automatically process the pulse oximetry plethysmograph to calculate indices based on stroke volume[14], and this could be also be used to assess fluid responsiveness. The device is based on a novel mathematical analytical process, which can potentially provide a continuous and automatic indirect measure of stroke volume/cardiac output. It does not rely on PI or PVI, but instead analyses the beat-to-beat changes in the area under the curve of the plethysmograph to reflect variations in stroke volume[15]. As the device is entirely non-invasive, it avoids the specific complications associated with PACs and other methods of cardiac output measurement. There are potential cost-savings in that the use of more expensive cardiac output measurement devices could be avoided. The ease of use associated with such a non-invasive device would allow more flexible usage and if it could reliably predict responsiveness to fluid

administration it may result in clinical benefits associated with devices which have already been shown to predict fluid responsiveness[16]. Differences between this device and the NICOM device are summarised in Table 1.

In this study, two hypotheses were tested: (i) that the output from this prototype device correlates with pulmonary artery catheter measurements of cardiac output or stroke volume via the continuous thermodilution technique; and (ii) that the this device can be used to predict those patients who would respond to a fluid bolus as indicated by a rise in stroke volume of 10% or more as recorded by a pulmonary artery catheter.

5.3.Methods

The study was registered with the Australian New Zealand Clinical Trials Registry with the reference number ACTRN12612000770864. Following local institutional (Research Office, Auckland City Hospital; registration number A+5549) and national (New Zealand Health and Disability Ethics Committee; registration number NTX/12/06/058/AM05) ethical committee approval and having obtained written informed consent from each, 20 adult patients scheduled to undergo elective cardiac surgery where the use of a pulmonary artery catheter for cardiac output monitoring was deemed necessary were recruited for this prospective study at Auckland City Hospital, Auckland, New Zealand between October 2013 and March 2016. The sample size of 20 patients was selected based on a power analysis in a previous study[17] which found that 19 patients were needed to detect a difference of 0.3 in the areas under the receiver operating characteristic (ROC) curves between the standard method and the test method (alpha 0.05, beta 0.2), and other studies[18, 19].

Exclusion criteria were patient refusal (or inability to provide informed consent), left ventricular ejection fraction less than 30%, cardiac rhythm other than sinus rhythm, known moderate (or worse) tricuspid or aortic regurgitation (which can lead to inaccuracies in thermodilution estimates

of CO or inconsistencies in the plethysmograph respectively), the use of an intra-aortic balloon pump or the known presence of haemoglobinopathy.

Each patient's age, gender, height, weight, and body mass index were recorded. Following instigation of routine monitoring, and insertion of an arterial line for invasive blood pressure monitoring, anaesthesia was induced. A central venous catheter was inserted in the right internal jugular vein and a pulmonary artery catheter was inserted and positioned appropriately. The novel device (ND) was placed on an appropriate finger. Once cardiac index (CI) had stabilised, baseline haemodynamic data (heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP) and CI), and the reading from the novel device were recorded three times at one minute intervals. CI was recorded using a Vigilance II Patient Monitor (Edwards Lifesciences, Irvine, CA, USA). Investigators were blinded to the output from the novel device until the data was extracted from the device following completion of the entire study.

A crystalloid fluid bolus (Plasma-Lyte 148, Baxter International Inc., Deerfield, IL, USA) of 7 $ml.kg^{-1}$ at 1 $ml.kg^{-1}.min^{-1}$ (based on previous studies[19]) was administered. A repeat set of haemodynamic readings was taken two minutes following completion of the fluid bolus, three times at

one minute intervals. No other fluids or vasopressors were administered during this period, and no changes were made to the ventilatory settings. For each reading, before and after the fluid bolus, cardiac output (CO) and stroke volume (SV) were calculated for each corresponding CI. Readings of CI taken from the PAC using the continuous thermodilution technique were considered the reference technique. Patients were considered 'responders' to the fluid bolus if their calculated SV increased by 10% or more (as per Hood et al[20]).

Precision of the reference technique (for CO) was calculated using the three consecutive readings taken each time. An inter-patient coefficient of variation (2SD/mean) lower than 30% was considered an acceptable limit a priori[21, 22]. Scatter plots were constructed using mean values of three readings both before and after the fluid bolus for the comparisons of CI vs. ND and SV vs. ND. Lines of equality were plotted and Pearson's correlation coefficient was calculated in each case. A receiver operating characteristic (ROC) curve was constructed for the ability (or otherwise) of the novel device to predict fluid responsiveness, and the area the ROC curve (AUROC) was calculated. All data were recorded on case record forms and subsequently inputted into both Excel (Microsoft, Redmond, WA, USA) for analysis and graphs were prepared using Stata: Version 13.1 (StataCorp LP, College Station, TX, USA).

5.4. Results

In total, 25 patients were approached for possible participation in the study. Two patients declined to take part. One patient developed atrial fibrillation immediately following induction of anaesthesia and so was excluded from the study without taking any readings or giving the fluid bolus. A further patient was excluded following completion of our readings as they were unexpectedly found to have severe tricuspid regurgitation on intraoperative transoesophageal echocardiography. A final patient was excluded prior to any readings or fluid bolus administration as the novel device failed to function. Baseline characteristics of the 20 completed study cases are summarised in Table 2. During analysis of the data recorded by the novel device, it was found that data belonging to two patients were missing and so only 18 patients' completed readings were used for production of our graphs and comparative analysis. Of these patients, 7 (39%) were identified as responders to the fluid bolus.

Precision of the reference technique is shown in Table 3 and is within the acceptable a priori limit. Precision of the novel device is included for comparison. Scatter plots with regression lines comparing the correlation between the novel device (including data from before and following the fluid bolus) and both CO and SV are shown in Figure 1 with the

corresponding value of linear regression coefficient (r^2). The ROC curve along with the area under the ROC curve for the ability of the novel device to predict the responsiveness to fluid is shown in Figure 2. Cohen's kappa was 0.16 which indicates slight agreement between the methods in predicting fluid responsiveness[23].

Although recommended by Critchley et al[24], polar plots were not produced as to do so requires that both methods utilise the same units of measurement, which is not the case in this study. For the same reason it was not possible to use Perrino et al's[25] four-quadrant plots.

5.5. Discussion

The results of this study show that the novel device correlated poorly with both CO and SV measured from the reference technique, with an r^2 of 0.0145 and 0.0558 respectively (Figure 1). In addition, the area under the ROC curve (AUROC) was 0.5844 which confirms that the novel device is not useful in the prediction of responsiveness to a fluid bolus of this type and size in this population. The AUROC improves to 0.614 when the log of the output from the novel device is used for analysis (not shown). Consequently, both hypotheses can be rejected.

To the authors' best knowledge, this is the first study using this particular method of non-invasively identifying fluid responsiveness and therefore no previously published work exists to allow comparison in this regard. Also, there are no major publications featuring investigations into automated methods of calculating POPV. The initial studies of this device were proof-of-concept studies[14, 15]. The authors did not specify the number of patients studied, other than stating that some were intensive care patients (which comprised 'stable' and 'unstable' patients) and others were patients undergoing dialysis. The data from these patients was not summarised or analysed in any meaningful way, and indeed one graph used in each paper appeared to be the same. As such, it is difficult

to draw conclusions from these papers as to how accurate or reliable the device might be.

However, other studies investigating plethysmographic waveform analysis have shown some promise. Chu et al[26] produced a systematic review into the use of Masimo's Pleth Variability Index (PVI) for the prediction of fluid responsiveness in ventilated patients in 2016. They found a pooled AUROC of 0.88 for the 18 trials included, which would indicate that PVI is useful for the prediction of fluid responsiveness in these patients. A further and more recent systematic review of 25 studies confirmed this result[27]. Both these reviews found no heterogeneity between the included studies. In a large review published in 2018, Messina et al[28] stated that the reliability of both PPV and SVV in predicting fluid responsiveness was limited with a high degree of heterogeneity.

Of note, Cannesson et al[29] described a 'gray zone' in which fluid responsiveness cannot be predicted in 25% of patients during GA and that this 'gray zone' needs to be defined for each dynamic index used to predict fluid responsiveness. This does not yet appear to have been accounted for in major studies of such indices.

Our study was limited by its small size. Although precision of the reference technique is within the a priori limits of 30%, the precision of the novel device is poor and this would undoubtedly have led to the poor performance of the device overall. The reasons for the poor precision are not clear, but it could be due to the fact that the device was not covered to protect it from interference from ambient lighting in the theatre, or due to electromagnetic interference from other sources within the operating theatre environment. One of the steps taken by the developers to prevent interference was to place a signal processor along the lead closer to the light receptor and point of origin of the signal, although the effectiveness of this has not been measured to date. Notwithstanding the small sample size, the overall response to the fluid bolus was low (39%) and was negative in many cases. Other studies assessing fluid responsiveness have documented responses of approximately 50%[29]. This smaller number of responders makes it less likely that any device would detect fluid responsiveness. A further problem is that there does not appear to be a clear definition of what constitutes a positive response to a fluid bolus. Messina's review article[28] clearly demonstrates this problem with the included studies defining a response as increases in SV of greater than or equal to 5%, 10%, 12%, 15%, 20%, and 25%. Other studies have relied upon changes in CI[30, 31], CO[29], or MAP (via changes in CO)[32]. According the Squara et al[22], numbers displayed by pulmonary artery catheter continuous cardiac

output (PAC CCO) devices represent the average of at least the five previous readings, each taken as a 1-minute running average. This diminishes the time response of the device to actual change in CO and it may be that the reference technique in our study did not physically have enough time to detect responders to the fluid bolus. Despite this, Squara notes that the PAC CCO remains the most commonly used reference technique in fluid responsiveness studies. Finally, the ROC curve approach does not take into account the existence of an overlap between responders and non-responders[33], something analogous to Cannesson's 'gray zone' discussed earlier[29].

While ongoing research continues to indicate that PVI may be a useful tool for the prediction of fluid responsiveness, the novel device requires technical refinement before it could be considered for further study.

The results of this investigation indicate that the novel device is currently not suitable for use in the measurement of stroke volume or as a tool to predict fluid responsiveness.

Acknowledgements

Prof. George Shorten of both the Department of Anaesthesia and Intensive Care Medicine at Cork University Hospital, and University College Cork, Ireland, provided advice regarding the conduct of the

study. Associate Professor Tim Short and Prof. Alan Merry, both of Auckland City Hospital and The University Of Auckland, New Zealand, provided advice and assistance in the completion of the study.

Competing Interests

This work was supported by a grant from Auckland District Health Board Trust. The University of Limerick has applied for patents in respect of the novel device. None of the authors hold any patents in relation to the device.

5.6. Tables

Table 1. Similarities and differences between the novel device and the NICOM.

Novel Device	NICOM
Non-invasive	Non-invasive
Continuous	Continuous
Measurements derived from photoplethysmography	Measurements derived from bioimpedence
Single finger clip sensor placed over a single digit	Four pads placed on the thorax, each containing an electrode (emitter) and a sensor
Published algorithm	Proprietary algorithm
Prototype phase	FDA-approved

Table 2. Summary of patients' characteristics and type of surgery. Values are number, median (IQR [range]) or number (proportion).

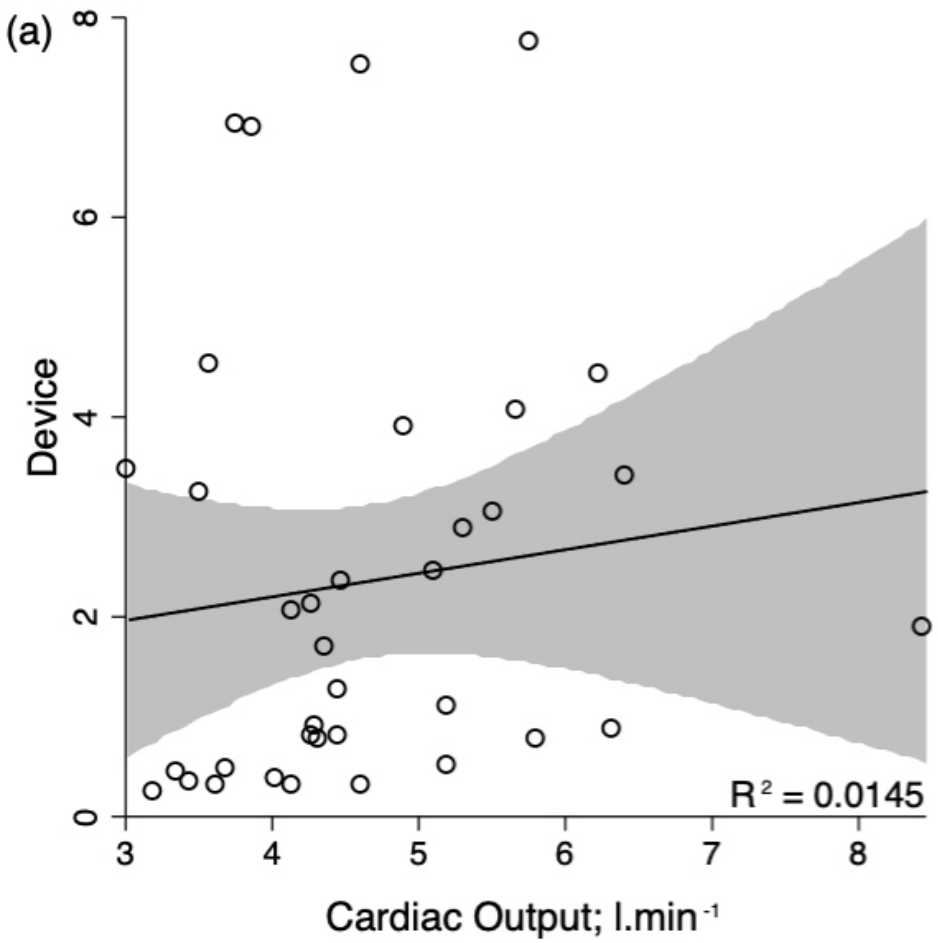
Number of subjects	20
Age; years	64.5 (61.5-72.25 [39-80])
Gender; M: F	13 : 7
Height; cm	166 (162.75-172.25 [155-187])
Weight; kg	76 (72.13-81.40 [61-108])
Body Mass Index; $kg.m^{-2}$	1.88 (1.81-1.95 [1.63-2.23])
Coronary Artery Bypass Graft	14 (70%)
Coronary Artery Bypass Graft & Mitral Valve Repair	2 (10%)
Mitral Valve Repair	1 (5%)
Mitral Valve Replacement	1 (5%)
Aortic Valve Replacement	1 (5%)
Coronary Artery Bypass Graft & Aortic Valve Replacement	1 (5%)

Table 3. Coefficients of Variation for reference technique measurements of cardiac output and stroke volume, and the Novel device.

	Cardiac Output	Stroke Volume	Novel Device
Pre-bolus; %	15.06	15.87	64.76
Post-bolus; %	9.65	13.55	46.76
Mean; %	12.36	14.71	55.76

5.7. Figures

Figure 1 (following page). Scatter plots for the comparisons between the novel device, and (a) cardiac output and (b) stroke volume. The shaded areas represent the 95% confidence intervals around the lines of regression. r^2 is displayed accordingly.


(a)
Device
Cardiac Output; l.min-1
R2 = 0.0145
0
2
4
6
8
3
4
5
6
7
8

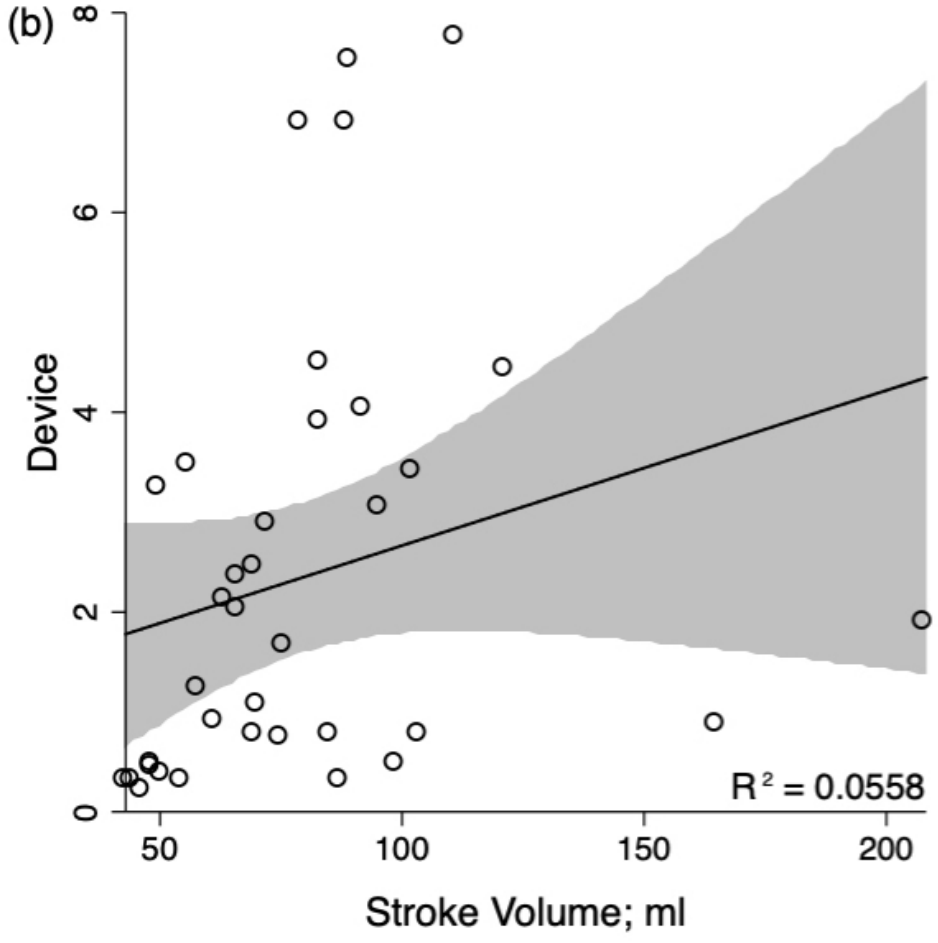
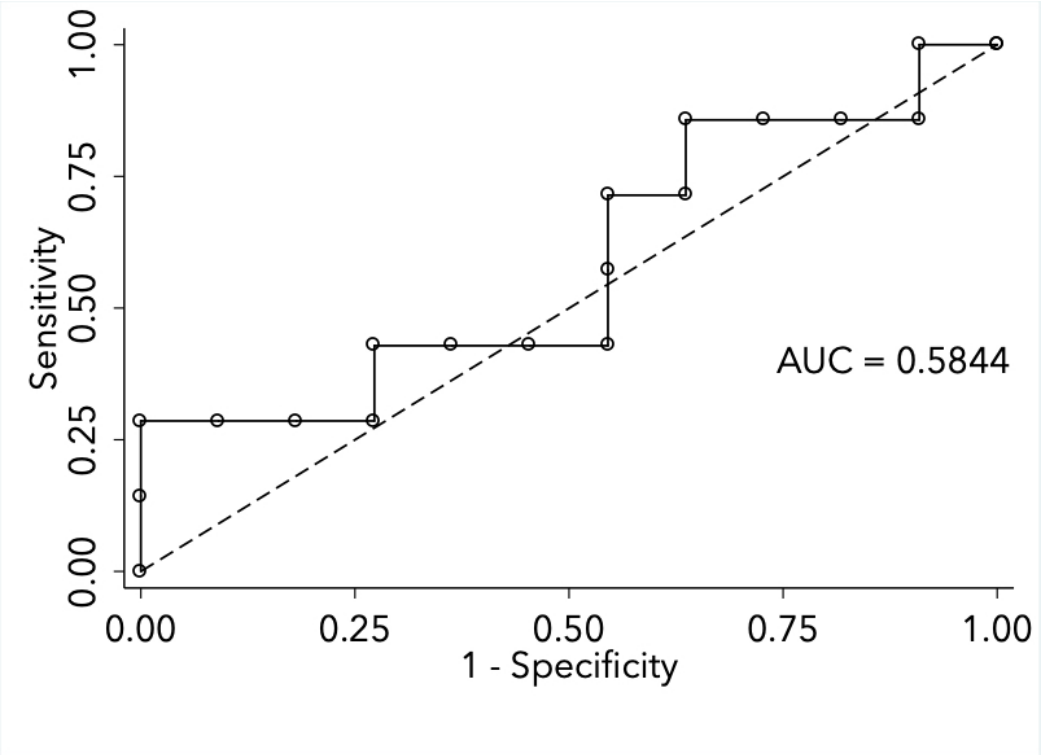

(b)
Device
Stroke Volume; ml
R2 = 0.0558
0
2
4
6
8
50
100
150
200

Figure 2. Receiver operating characteristic (ROC) curve for the ability of the novel device to predict fluid responsiveness as detected by a 10% (or greater) increase in stroke volume. Area under the ROC curve (AUC) is displayed.



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6.Conclusions

6.1.Clinical implications and future directions – studies 1 and 2

Study 1 – Clinical evaluation of a novel technology for the non-invasive and continuous measurement of plasma haemoglobin concentration.

Study 2 – Clinical evaluation of a novel device for the non-invasive and continuous measurement of haemoglobin in the obstetric population.

The principal findings from these studies show that this novel device, in its current form, is not a suitable method of measurement of haemoglobin compared to the commonly used reference methods (laboratory full blood count) in either patients undergoing cardiac surgery or pregnant patients.

The studies have some strengths: the assessment of repeated measures in the same patients (study 1, analysed as per Bland and Altman[1]), and the large number of patients assessed for inter-patient variability (study 2). However, the limitations were the small number of patients included in study 1, and the narrow range of haemoglobin values (IQR 110.8-124 $g.l^{-1}$) in study 2.

The United States Food and Drug Administration (FDA) defines process validation as "establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications"[2]. The clinical result of the novel device must be the accurate and reliable identification of patients in need of a blood transfusion. As this device does not consistently produce the intended results, it is appropriate to conclude that this device would fail process validation and therefore would not be suitable for clinical use.

Masimo Corporation (Irvine, California, USA) have developed a similar technology, now incorporated into several devices, which non-invasively and continuously measures haemoglobin. There are now many published studies confirming the accuracy and reliability of this technology. Most recently, this technology was shown to more accurately estimate the timing for invasive haemoglobin measurements than clinicians[3], and also to result in cost savings by significantly reducing the need for blood transfusion[4]. As most of the information regarding the functioning of Masimo's device is unknown, one can only assume that the reasons behind its improved performance compared with the novel device of this thesis is that it uses wavelengths of light more suited to the measurement of haemoglobin, that the algorithms used allow for a more accurate analysis of the waveforms and measurement of haemoglobin,

and that their correlation curves were calculated using data from large sample sizes across many physiological situations.

Wearable electronic monitoring devices are becoming cheaper and more common. Several wearable medical-grade devices, such as the FreeStyle Libre Flash system (Abbott Diabetes Care, Alameda, California, USA)[5], which allow continuous glucose monitoring have already received FDA approval. While the market is saturated with non-FDA approved heart rate monitors, some have received FDA approval, and one has received approval for the detection of atrial fibrillation[6]. It is likely simply a matter of time before a wearable device will receive approval for the measurement of haemoglobin.

In order to establish process validity, the novel device will require several refinements. These may include improvements to the processing algorithm, or to the hardware and software signal processing. Further studies with volunteers confirming an improved performance will then be needed before larger-scale clinical trials could hopefully establish process validity. However, given its poor performance to date, and the establishment of clinically acceptable alternative devices with the promise of further developments with miniaturised and cheaper devices, the novel device is not likely to have any future clinical role.

6.2.Clinical implications and future directions – study 3

Study 3 – Evaluation of a novel, non-invasive method for the estimation of stroke volume and the prediction of fluid responsiveness.

The principals findings of this study showed that this form of plethysmographic waveform variation analysis does not correlate well with either cardiac output or stroke volume and is not useful for the prediction of those patient who would respond appropriately to a fluid bolus.

Despite the findings, the study had numerous strengths. The study investigated not just simple correlation between the methods of measurement, but also the trend of the readings or the "degree of correct identification of response to (an) intervention" as recommend by Chikhani and Moppett in their 2011 editorial in the British Journal of Anaesthesia[7]. The novel device was compared with the commonly accepted "gold standard" of cardiac output monitoring using a pulmonary artery catheter and the thermodilution method and the precision of the gold standard was confirmed. The twenty participants recruited should have been enough to demonstrate at least some degree of correlation between the methods of measurement.

However, due to the unusually small number of fluid responders identified, twenty participants was probably not enough, in retrospect, to detect a sizeable number of responders. In addition, Squara identified a number of limitations in relation to continuous cardiac output monitoring using a pulmonary artery catheter (such as a poor time response) which might mean that true responders were not detected in the first place[8].

Some commentators have stated that precise measurements of cardiac output or stroke volume are not necessary or even helpful and that the focus of research should solely be on developing devices which can identify fluid responders[7, 9]. This could be assisted by using a different reference method where measurements of stroke volume are truly real-time (for example transoesophageal echocardiography, or a continuous cardiac output measurement device with better averaging[8]). This would be a goal worth pursuing, as such a validated, easy-to-use, and truly non-invasive trend monitor would hopefully lead to better outcomes in terms of decreased patient perioperative morbidity and/or mortality with potential cost-savings in reduced intensive care and ward level lengths of stay.

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7.Publications arising

A portion of Chapter 1 (Introduction) was published as an editorial in the journal Anaesthesia under the title "Point-of-care haemoglobin measurement - state of the art or a bleeding nuisance?"[1]

Chapter 2 (Study 1) was published as an original research article in the journal Anaesthesia with the title of "Clinical evaluation of a novel technology for non-invasive and continuous measurement of plasma haemoglobin concentration."[2]

Correspondence regarding Study 1 was published in the journal Anaesthesia[3, 4].

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8.Appendices

8.1.Original MD Submission

MD Proposal – Dr. Alan Broderick

Course Code: CKZ41

PAC Application Number: 11223719

Title of Proposed Work:

A novel, non-invasive, optical, device for the measurement of total haemoglobin and monitoring of stroke volume/fluid responsiveness – initial clinical evaluation.

Locations where work will be completed:

Cork University Hospital, Cork, Ireland.

Auckland City Hospital, Auckland, New Zealand.

Supervisors:

Dr. Dorothy Breen, Consultant Anaesthetist, Cork University Hospital

Dr. Sara Allen, Consultant Anaesthetist, Auckland City Hospital

Overall Objective:

To assess the accuracy and usability of a novel, non-invasive, optical device with regard to:

The device's measurement of total haemoglobin;

The device's measurement of indices reflecting stroke volume and trends in stroke volume variation following fluid challenges.

To achieve this, I propose to carry out three clinical studies.

(1). A prospective observational study examining the correlation between estimates of total haemoglobin concentration using i. the novel device and ii. a laboratory 'gold standard' (XE-2100, Sysmex Corp., Kobe, Japan) in patients undergoing cardiac surgery (a clinical setting associated with significant blood loss and haemodynamic fluctuations).

(2). A prospective observational study examining correlation between estimates of total haemoglobin concentration using i. the novel device and ii. a laboratory 'gold standard' (XE-2100, Sysmex Corp., Kobe, Japan) in patients presenting for their 20-week antenatal check-up (an elective outpatient clinical setting).

(3). A prospective observational study examining correlation between estimates of cardiac output using i. a modified version of the novel device and ii. a clinical 'gold standard' pulmonary artery catheter-based technique.

Background and Significance

Haemoglobin

In many clinical situations, haemoglobin concentrations need to be determined frequently and/or urgently (such as during cardiac or vascular surgery, in trauma patients or in the intensive care setting). This usually requires sampling and processing of blood either in the laboratory (formal Full Blood Count (FBC)), or with a point-of-care analyser (such as the GEM Premier 4000). A continuous, non-invasive and accurate method would allow for more rapid decision-making in these situations.

The Optical Fibre Sensor Research Centre at the University of Limerick (UL) together with the Institute of General Electrical Engineering at the University of Rostock, Germany have co-developed a device for the non-invasive, optical, real-time measurement of haemoglobin, which functions similar to a standard pulse-oximeter [1, 2]. A similar commercial device is available (Rainbow SET Pulse CO-Oximeter, Masimo Corporation, Irvine, CA, USA) which has been tested clinically with mixed results. Masimo's device is different in that it uses seven wavelengths of light, while the novel device uses just two wavelengths of light, which has a potential cost saving. Additionally, the device has been shown to

accurately measure very low haemoglobin concentrations in-vitro (38.7 $g.l^{-1}$)[3]. However, this device has yet to be tested clinically.

Haemodynamic monitoring

There is no gold standard for the clinical measurement of cardiac output, although the bolus thermodilution method has been accepted as a "practical" gold standard since the 1970s[4]. However, this method is associated with complications[5, 6]. Over the last number of years, various devices have been developed to allow measurement of cardiac output (PiCCO, LiDCO, Doppler oesophageal probes, partial CO_2 re-breathing, etc). Apart from bioimpedance methods (such as NICOM[7]), none of these methods are truly non-invasive.

A rapidly responding, automated and truly non-invasive measurement of fluid responsiveness would avoid the complications of more invasive methods, and could allow for easier goal-directed management of surgical patients.

It is known that the arterial pulse pressure variation (PPV), a system based on analysing the arterial pressure waveform, can reflect cardiac output and predict fluid responsiveness[8].

Studies have shown that the information derived from the pulse oximetry plethysmograph (the pulse oximetry plethysmograph variation or POPV) is as good as PPV for predicting fluid responsiveness[9] and is a reliable indicator of mild hypovolaemia in anaesthetised patients[10].

However, none of the POPV systems (which are no more invasive than a standard pulse oximetry probe) present automated data. Masimo have various devices, which measure pleth variability index (PVI). This calculates the variation in the perfusion index (PI) which is calculated from the formula PI=(AC/DC) x 100 (where AC is the varying portion of the light absorbance signal caused by pulsatile blood flow, and DC is the constant portion of the light absorbance signal caused by skin, muscle, tendon, bone, and venous (non-pulsatile) blood)[11]. Changes in PVI have been shown to reflect changes in POPV[11], and therefore has the potential to be used as a guide to fluid management of intraoperative patients[12].

The novel device non-invasively and automatically processes the pulse oximetry plethysmograph to calculate indices based on cardiac output/ fluid responsiveness[3]. The device is based on a novel mathematical analytical process, which potentially can provide a continuous and automatic indirect measure of cardiac output. It does not rely on PI or

PVI, but instead analyses the beat-to-beat changes in area-under-the-curve of the plethysmograph to calculate an index of stroke volume[13].

Device advantages

This device has the potential to offer many advantages over other similar devices, as presented in table 1 below. The device would be entirely non-invasive and therefore without the specific complications associated with both laboratory FBCs and other methods of cardiac output measurement. There are potential cost-savings in that fewer FBC tests could be ordered, or the use of more expensive cardiac output measurement devices could be avoided. The device itself utilises fewer wavelengths of light than Masimo's device, which has a potential cost-saving. The ease of use associated with such a non-invasive device would allow more flexible usage and if it could reliably predict responsiveness to fluid administration it may result in clinical benefits associated with systems which have already be shown to predict fluid responsiveness[14].

Table 1. Advantages and Disadvantages of Various Cardiac Output Monitors

	Advantage	Disadvantage
Pulmonary Artery Catheter (with bolus thermodilution method)	Considered the 'gold standard'	Invasive, complicated, associated with complications[5]
PiCCO (Pulsion Medical Systems AG, Munich, Germany)	Accurate, relatively easy to set up	Two invasive components, require calibration with thermodilution
LiDCO (LiDCO Ltd., Cambridge, UK)	Accurate, less invasive than the above	Requires arterial line and injection with lithium for calibration
Vigileo (Edwards Lifesciences, Irvine, CA, USA)	Does not require calibration	Requires arterial line
Oesophageal Doppler Ultrasound (various devices)	Considered semi-invasive, use may be beneficial[15]	Time-consuming, operator dependent, requires training[16]
Pulse Dye Densitometry[17] (PDD; DDG2001 analyzer, Tokyo, Japan)	Sensor is non-invasive	Requires injection of indocyanine green dye for calibration

	Advantage	Disadvantage
Bioimpedance Cardiography (various devices)	Non-invasive system	Conflicting results[18]
Pleth Variability Index (Masimo Corp., Irvine, CA, USA)	Non-invasive system	May improve fluid management, but no proven improved clinical outcome[12]

Study 1: Clinical validation of a novel device for the non-invasive continuous measurement of haemoglobin.

Co-investigators:

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Background and Significance

During cardiac surgery patients undergo large and rapid changes in total haemoglobin concentration secondary to blood loss, dilution (pump prime), or blood product transfusion at various points. Additionally, the institution of cardiopulmonary bypass (CPB) causes gross haemodilution, which is partially corrected following discontinuation of CPB. These cases present ideal opportunities to study fluctuations in haemoglobin within the same patient.

I propose to compare total haemoglobin concentration estimation using the novel device with i. the GEM Premier 4000 point-of-care analyser and ii. a standard laboratory device, in patients undergoing cardiac surgery.

Hypothesis

That a non-invasive, continuous pulse-haemoglobinometer can accurately and reliably measure haemoglobin concentration in patients undergoing cardiac surgery (with cardiopulmonary bypass).

Methods

The setting will be patients undergoing elective cardiac surgery involving cardiopulmonary bypass at Cork University Hospital. Following local ethical approval and with the informed written consent of each, 25 patients will be admitted to the study. Each will have the following baseline data recorded:

- Age
- Sex
- Weight
- Haemoglobin (a recent laboratory FBC)
- Temperature
- Smoking history (active/previous/non-smoking, pack years, date of cessation)
- Surgery to be carried out

Following induction of anaesthesia, the novel device will be fitted on the index finger of each patient's right hand (unless the right radial artery is to be used for grafting in which case the left index finger will be used). At four time points, an arterial blood sample will be taken and processed on the GEM Premier 4000 point-of-care analyser with a sample also being sent to the laboratory for FBC measurement. At these time points, the patient's total haemoglobin as displayed by the study device will also be noted.

Arterial samples will be taken as follows (using aseptic technique):

- 10cc of blood/hep-saline flush is drawn via the most distal port (i.e. that closest to the patient)
- 6cc of blood is then drawn and 4.1cc is transferred to a standard Li-Heparin blood sample bottle (for the laboratory FBC)
- The remaining blood is transferred into an arterial blood gas syringe which is then processed using the GEM Premier 4000
- Having ensured no air bubbles are present in the system, the arterial line is flushed using the arterial line flushing mechanism until clear of blood
- The original 10cc of blood/hep-saline is returned to the patient via a peripheral line

The time points shall be:

- At skin incision (start of surgery)
- Two minutes following completion of first dose of heparin (pre-CPB)
- Two minutes following completion of administration of the first dose of protamine (post-CPB)
- At completion of final skin suture (end of surgery)

The laboratory FBC will be considered the gold standard. A bivariate plot will be constructed and Pearson's Correlation Coefficient, r will be calculated for the following comparisons;

- Novel device vs. laboratory FBC (primary outcome)
- Novel device vs. GEM Premier 4000
- GEM Premier 4000 vs. laboratory FBC

Each will be tested for significance ($p<0.05$) and tested for agreement using the Bland-Altman method[19] as appropriate.

Study 2: Clinical validation of a novel device for the non-invasive measurement of haemoglobin in the obstetric population.

Co-investigators:

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Background and Significance

The World Health Organization has reported that 18% of pregnant women from industrialized countries have iron-deficiency anaemia[20]. Pregnant patients attending antenatal clinics frequently undergo blood sampling for haemoglobin measurement. This is an invasive procedure involving venepuncture (painful) with the possibility of infection, and the results are not usually available until some time later. At present, all pregnant women booked into Cork University Maternity Hospital have a FBC taken at the 20-week antenatal check. Most of these women would also have FBCs sent by their general practitioner prior to booking, and all those considered to be at risk will have more frequent blood sampling. A non-invasive, point-of-care device would allow for

unrestricted, painless and risk-free rapid haemoglobin assessment, while decreasing the cost of processing blood samples. Earlier and more frequent sampling may also allow for more timely iron supplementation in those found requiring such treatment.

Hypothesis

That a non-invasive, continuous pulse-haemoglobinometer can accurately and reliably estimate haemoglobin concentration in patients attending an out-patient antenatal clinic for the 20-week check-up.

Methods

The setting will be obstetric patients presenting electively for their 20-week check-up at the outpatient antenatal clinics, who are routinely having a blood sample drawn for a FBC. Following local ethical approval and with the informed written consent of each, 100 such patients will be admitted to the study and will have the following baseline data recorded:

- Age
- Sex
- Weight
- Temperature

- Smoking history (active/previous/non-smoking, pack years, date of cessation)

The novel device will be placed on the index finger of the opposite upper limb to that being used for blood sampling. This is to avoid any concerns about the tourniquet interfering with light absorption in the device. Whichever hand is used will be briefly covered in a light proof material similar to a glove in order to minimise interference from ambient light. The device will be left in place for one minute in order for it to stabilise its reading. As the blood sample is drawn, the haemoglobin as measured by the device will be noted.

The laboratory FBC will be considered the gold standard. A bivariate plot will be constructed and Pearson's Correlation Coefficient, r will be calculated for the novel device against the laboratory FBC. This will be tested for significance ($p<0.05$) and further testing using the Bland-Altman method[19], and/or calculation of bias and precision will be carried out as appropriate.

Study 3: A novel, non-invasive device for the detection of a response to a fluid challenge - comparison with bolus thermodilution in elective coronary artery bypass grafting patients.

Co-investigators:

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†Optical Fibre Research Centre, University of Limerick, Limerick, Ireland

*Cork University Hospital, Cork, Ireland

‡Auckland City Hospital, Auckland, New Zealand

Hypotheses

(1)That a novel, automated, non-invasive device analysing the pulse oximetry plethysmographic waveform can correlate with cardiac output (as measured using the bolus thermodilution method) in anaesthetised, ventilated and haemodynamically stable patients about to undergo coronary artery bypass grafting

(2)That this novel, automated, non-invasive device can detect a positive response (measured as an increase in a marker of stroke volume/cardiac output), or lack thereof, to a fluid bolus in anaesthetised, ventilated and haemodynamically stable patients about

to undergo coronary artery bypass grafting (as detected using the bolus thermodilution method).

Methods

This will be a prospective study involving 20 patients scheduled for coronary artery bypass grafting at Auckland City Hospital, Auckland, New Zealand, who would ordinarily have a pulmonary artery catheter (PAC) inserted. Full informed consent will be obtained from each participant.

Following attachment of routine monitors, and insertion of an arterial line for invasive blood pressure monitoring, anaesthesia will be induced and a pulmonary artery catheter will be inserted. The novel device will be placed on an appropriate finger. After a period of 15 minutes without adjustment in vasopressor/inotrope infusion rates, ventilation settings, or fluid delivery, a baseline reading for cardiac output (CO) will be taken from the PAC in accordance with the manufacturers guidelines. At the same time, the reading from the novel device will be recorded. A fluid bolus of colloid (7mL/kg at 1mL/kg/min) will be given, and a second set of haemodynamic readings will be taken.

The values for cardiac output will be compared using the Bland-Altman method[19]. Bias, precision and correlation will also be assessed. Polar

plots will be presented to demonstrate trending ability, as suggested by Critchley[21].

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8.2.Protocol for Study I

DETAILED PROTOCOL FOR:

Clinical validation of a novel device for the non-invasive continuous measurement of haemoglobin.

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Introduction

In many clinical situations, haemoglobin concentrations need to be determined frequently and /or urgently (such as during cardiac or vascular surgery, in trauma patients or in the intensive care setting). This usually requires sampling and processing of blood either in the laboratory (formal Full Blood Count (FBC)), or with a point-of-care analyser (such as the GEM Premier 4000). A continuous, non-invasive and accurate method would allow for more rapid decision-making in these situations.

The Optical Fibre Sensor Research Centre at the University of Limerick together with the Institute of General Electrical Engineering at the University of Rostock, Germany have co-developed a device for the non-invasive, optical, real-time measurement of haemoglobin, which functions similar to a standard pulse-oximeter[1, 2]. Such devices have been developed before, such as the Rainbow SET Pulse CO-Oximeter (Masimo Corporation, Irvine, CA, USA), but no clinical validation studies of such devices have been published fully in peer-reviewed scientific journals.

Patients undergoing cardiac surgery undergo large and rapid changes in total haemoglobin concentration secondary to blood loss, dilution (pump prime), or blood product transfusion at various points. Additionally, the institution of cardiopulmonary bypass (CPB) causes gross haemodilution, which is partially corrected following discontinuation of CPB. These cases present ideal opportunities to study fluctuations in haemoglobin within the same patient.

Objectives

To compare total haemoglobin concentration estimation using the novel device with i. the GEM Premier 4000 point-of-care analyser and ii. a standard laboratory device, in patients undergoing cardiac surgery.

Outcomes

Total haemoglobin as measured at four time points by the study device, the GEM Premier 4000 and the haematology laboratory.

Study Design

A prospective correlation study.

Sample Size

An arbitrary sample size of 25 patients will be used, with 4 samples taken from each patient (therefore resulting in 100 data points).

Inclusion Criteria

- Age >18
- Patients undergoing any cardiac surgery which will involve cardiopulmonary bypass

Exclusion Criteria

- Patient refusal or inability to provide consent

- Any haemoglobinopathy (e.g. methaemoglobinaemia, sickle cell disease, thalassaemia)
- Recent dye/contrast studies

Methods

Baseline data

Following local ethical approval and with the informed written consent of each, patients admitted to the study will have the following baseline data recorded;

- Age
- Sex
- Weight
- Haemoglobin (laboratory FBC from within the previous 24 hours)
- Temperature
- Smoking history (active/previous/non-smoking, pack years, date of cessation)
- Surgery to be carried out

Setting

The cardiothoracic operating theatres (numbers 1 and 1A) at Cork University Hospital. All blood samples will be collected in theatre. Following induction of anaesthesia, the novel device will be fitted on the index finger of the each patient's right hand (unless the right radial artery is to be used for grafting in which case the left index finger will be used). Blood drawn for the study shall be analysed using the GEM Premier 4000 point-of-care device located in theatre 1A only (i.e. the same device each time) and also sent to the haematology laboratory for standard FBC measurement.

Intervention

At four time points, an arterial blood sample will be taken and processed on the GEM Premier 4000 point-of-care analyser with a sample also being sent to the laboratory for FBC measurement. At these time points, the patient's total haemoglobin as displayed by the study device will also be noted. In addition, at the first time point a blood sample will also be taken from the patient's central line for measurement via the GEM Premier 4000 and sent to the laboratory for FBC measurement.

Arterial samples will be taken as follows (using aseptic technique);

- 10cc of blood/hep-saline flush is drawn via the most distal port (i.e. that closest to the patient)
- 6cc of blood is then drawn and 4.1cc is transferred to a standard Li-Heparin blood sample bottle (for the laboratory FBC)
- the remaining blood is transferred into an arterial blood gas syringe which is then processed using the GEM Premier 4000
- having ensured no air bubbles are present in the system, the arterial line is flushed using the arterial line flushing mechanism until clear of blood
- the original 10cc of blood/hep-saline is returned to the patient via a peripheral line

The time points shall be:

- At skin incision (start of surgery)
- Two minutes following completion of first dose of heparin (pre-CPB)
- Two minutes following completion of administration of the first dose of protamine (post-CPB)
- At completion of final skin suture (end of surgery)

Assays

- The novel device
- GEM Premier 4000 (Instrumentation Laboratory, Bedford, MA, USA)
- Laboratory FBC device

Data management

The laboratory FBC will be considered the gold standard. A bivariate plot will be constructed and Pearson's Correlation Coefficient, r will be calculated for the following comparisons;

- Novel device vs. laboratory FBC (primary outcome)
- Novel device vs. GEM Premier 4000
- GEM Premier 4000 vs. laboratory FBC

Each will be tested for significance ($p<0.05$) and tested for agreement using the Bland-Altman method[3].

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8.3.Protocol for Study II

DETAILED PROTOCOL FOR:

Clinical validation of a novel device for the non-invasive measurement of haemoglobin in the obstetric population.

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†Optical Fibre Sensor Research Centre, University of Limerick

Introduction

In many clinical situations, haemoglobin concentrations need to be determined frequently and/or urgently (such as during cardiac or vascular surgery, in trauma patients or in out-patient situations such as ante-natal clinics). This usually requires sampling and processing of blood either in the laboratory (formal Full Blood Count (FBC)), or with a point-of-care analyser. A continuous, non-invasive and accurate method would allow for more rapid decision-making in these situations.

The Optical Fibre Sensor Research Centre at the University of Limerick (UL) together with the Institute of General Electrical Engineering at the University of Rostock, Germany have co-developed a novel device for the non-invasive, optical, real-time measurement of haemoglobin, which functions similar to a standard pulse-oximeter[1, 2].

A similar commercial device is available (Rainbow SET Pulse CO-Oximeter, Masimo Corporation, Irvine, CA, USA) which has been tested clinically with mixed results, however there have been no published data on out-patients (obstetric or otherwise). Masimo's device uses seven wavelengths of light, while the novel device uses just two wavelengths of infrared light, which has a potential cost saving. Also, the novel device has been shown to accurately measure very low haemoglobin concentrations in-vitro (38.7 $g.l^{-1}$)[3]. However, this device has yet to be tested clinically.

The World Health Organization has reported that 18% of pregnant women from industrialized countries have iron-deficiency anaemia[4]. Pregnant patients attending antenatal clinics frequently undergo blood sampling for haemoglobin measurement. This is an invasive procedure involving venepuncture (painful) with the possibility of infection, and the results are not usually available until some time later. At present, all pregnant women booked into Cork University Maternity Hospital have a

Full Blood Count (FBC) taken at the 20-week antenatal check. Most of these women would also have FBCs sent by their general practitioner prior to booking, and all those considered to be at risk will have more frequent blood sampling. A non-invasive, point-of-care device would allow for unrestricted, painless and risk-free rapid haemoglobin assessment, while decreasing the cost of processing blood samples. Earlier and more frequent sampling may also allow for more timely iron supplementation in those found requiring such treatment.

Objectives

To compare total haemoglobin concentration estimation using the novel device with a standard laboratory device (XE-2100 Sysmex Corp., Kobe, Japan), in patients presenting for the 20-week antenatal check-up.

Hypothesis

A non-invasive, continuous pulse-haemoglobinometer can accurately and reliably estimate haemoglobin concentration in patients attending an out-patient antenatal clinic for the 20-week check-up.

Outcomes

Total haemoglobin as measured non-invasively by the study device, and invasively by the haematology laboratory in patients having routine blood sampling at 20 weeks' gestation.

Study Design

A prospective correlation study.

Sample Size

An arbitrary sample size of 100 patients will be used, resulting in 100 data points for analysis.

Inclusion Criteria

- Age 18
- Voluntarily presenting to the ante-natal clinic at CUMH for the 20 weeks' gestation check-up

Exclusion Criteria

- Patient refusal or inability to provide consent
- Any haemoglobinopathy (e.g. methaemoglobinaemia, sickle cell disease, thalassaemia)

- Acrylic nail polish/coverings (interferes with light absorption by device)
- Recent dye/contrast studies

Methods

Baseline data

Following local ethical approval and with the informed written consent of each, patients admitted to the study will have the following baseline data recorded;

- Age
- Sex
- Weight
- Temperature
- Smoking history (active/previous/non-smoking, pack years, date of cessation)

Setting

The antenatal clinics at Cork University Maternity Hospital.

Intervention

The novel device will be placed on the index finger of the opposite upper limb to that being used for blood sampling. This is to avoid any concerns about the tourniquet interfering with light absorption in the device. Whichever hand is used will be briefly covered in a light proof material similar to a glove in order to minimise interference from ambient light. The device will be left in place for one minute in order for it to stabilise its reading. As the blood sample is drawn, the haemoglobin as measured by the device will be noted.

Assays

- The novel device
- Laboratory FBC device (XE-2100)

Data Management

The laboratory FBC will be considered the gold standard. A bivariate plot will be constructed and Pearson's Correlation Coefficient, r will be calculated for the novel device against the laboratory FBC. This will be tested for significance ($p<0.05$) and tested for agreement using the Bland-Altman method[5].

References

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8.4. Protocol for Study III

DETAILED PROTOCOL FOR:

A novel, non-invasive device for the estimation of stroke volume – comparison with continuous thermodilution technique

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Introduction

There is no gold standard for the clinical measurement of cardiac output and stroke volume, although the bolus thermodilution technique via pulmonary artery catheters (PACs) has been accepted as a "practical" gold standard since the 1970s[1]. However, this technique is associated with complications[2, 3] and inherent error of up to 20%[1]. The continuous thermodilution cardiac output (CCO) technique has been shown to agree clinically with the bolus thermodilution technique in several studies[4, 5]. Over the last number of years, various devices have been developed to

allow measurement of cardiac output and stroke volume (PiCCO, LiDCO, Doppler oesophageal probes, partial CO_2 re-breathing, etc). Apart from bioimpedance methods (such as NICOM[6]), none of these methods are truly non-invasive.

A rapidly responding, automated and truly non-invasive measurement of cardiac output, stroke volume or fluid responsiveness would avoid the complications of more invasive methods, and could allow for easier goal-directed management of surgical patients.

It is known that the arterial pulse pressure variation (PPV), a system based on analysing the arterial pressure waveform, can reflect cardiac output and predict fluid responsiveness[7].

Studies have shown that the information derived from the pulse oximetry plethysmograph (pulse oximetry plethysmograph variation or POPV) is as good as PPV for predicting fluid responsiveness[8] and is a reliable indicator of mild hypovolaemia in anaesthetised patients[9]. However, none of the POPV systems (which are no more invasive than a standard pulse oximetry probe) present automated data.

Masimo have developed various devices, which measure the "plethysmograph variability index" or PVI. PVI is a measure of the

variation in the perfusion index (PI) which is calculated from the formula PI=(AC/DC) x 100 (where AC is the varying portion of the light absorbance signal caused by pulsatile blood flow, and DC is the constant portion of the light absorbance signal caused by skin, muscle, tendon, bone, and venous (non-pulsatile) blood)[10]. Changes in PVI have been shown to reflect changes in POPV[10], and therefore has the potential to be used as a guide to fluid management of intraoperative patients[11].

The Optical Fibre Sensor Research Centre at the University of Limerick (UL) together with the Institute of General Electrical Engineering at the University of Rostock, Germany have co-developed a novel device which has the potential to non-invasively and automatically process the pulse oximetry plethysmograph to calculate indices based on stroke volume/ fluid responsiveness[12]. The device is based on a novel mathematical analytical process, which potentially can provide a continuous and automatic indirect measure of stroke volume/cardiac output. It does not rely on PI or PVI, but instead analyses the beat-to-beat changes in the area-under-the-curve of the plethysmograph to reflect stroke volume[13].

As the device is entirely non-invasive, it avoids the specific complications associated with PACs and other methods of cardiac output measurement. There are potential cost-savings in that the use of more expensive cardiac output measurement devices could be avoided. The

ease of use associated with such a non-invasive device would allow more flexible usage and if it could reliably predict responsiveness to fluid administration it may result in clinical benefits associated with systems which have already be shown to predict fluid responsiveness[14].

Objectives

To examine whether there is a correlation between the indices of cardiac output/stroke volume as measured by the novel device and the cardiac index as measured by the continuous thermodilution technique.
To examine the relationship between increases in cardiac index (continuous thermodilution technique) following a fluid bolus and increases in such indices of cardiac output/stroke volume as measured by the novel device.

Hypothesis

That the displayed analysis the pulse oximetry plethysmographic waveform by a novel, automated, non-invasive device can correlate with cardiac output/stroke volume (as measured using the continuous thermodilution technique) in anaesthetised, ventilated and haemodynamically stable patients about to undergo cardiac surgery.

That this novel, automated, non-invasive device can detect a positive response (measured as an increase in a marker of stroke volume/cardiac output), or lack thereof, to a fluid bolus in anaesthetised, ventilated and haemodynamically stable patients about to undergo cardiac surgery (as detected using the continuous thermodilution technique).

Study Design

A prospective observational study.

Setting

This study will take place entirely at Auckland City Hospital, Auckland, New Zealand. Patients enrolled will be those undergoing cardiac surgical procedures who, in the opinion of the attending anaesthetist, require a pulmonary artery catheter (PAC) to be inserted prior to commencement of the procedure as part of their ordinary management.

Sample Size

A sample size of 20 patients has been chosen, based on previous studies[15-17].

Inclusion Criteria

- Age>18
- Patients due to undergo cardiac surgery
- PAC required to be inserted prior to commencement of surgery

Exclusion Criteria

- Patient refusal (or inability to provide full informed consent)
- Ejection fraction <30% (avoids potential difficulties with giving the fluid bolus)
- Cardiac arrhythmias present at induction
- Known moderate (or worse) tricuspid regurgitation (makes thermodilution estimates of CO inaccurate)
- Known moderate (or worse) aortic regurgitation (previous studies using pulse contour analysis have excluded these – causes an abnormal pulse signal)
- Presence of an intra-aortic balloon counterpulsation device (cause an abnormal pulse signal, device may give inaccurate readings)
- Known haemoglobinopathy (device will not read correctly)

Methods

Baseline data

Following local ethical approval and with the informed written consent of each, patients admitted to the study will have the following baseline data recorded:

- Age
- Sex
- Weight
- Temperature

Intervention

Following attachment of routine monitors, and insertion of an arterial line for invasive blood pressure monitoring, anaesthesia will be induced and a pulmonary artery catheter will be inserted. The novel device will be placed on an appropriate finger. Once cardiac index (CI) has stabilised, baseline haemodynamic data (HR, MAP, CVP, CI (the three latest readings), and the reading from the novel device) will be recorded. A fluid bolus of crystalloid (Plasma-Lyte 148) (7mL/kg at 1mL/kg/min, based on previous studies[17]) will be given. A second set of haemodynamic readings will be taken two minutes following completion of the fluid bolus. No changes to ventilatory settings, rates of inotrope/vasopressor delivery (if any), or rate of IV fluid administration (other than the fluid bolus) will be made between data recording points. In addition, no

supplemental vasoactive drugs will be given between data recording points.

Data Management

Readings of CI taken from the PAC using the continuous thermodilution technique will be considered the 'gold standard'. The precision of the PAC will be determined using the three consecutive readings taken each time. Scatter plots will be constructed of CI (from the PAC) against the readings from the novel device and linear regression analysis performed. Pearson's correlation coefficient will be calculated. Polar plots will be presented to demonstrate trending ability, as suggested by Critchley et al[18].

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8.5.Data Set for Study I

Key to Data Set

N = data missing

N/A = variable has no units or value is continuous/not defined

Variable Name	Variable Label	Units	Variable Values
No	Patient Number	N/A	N/A
Age	Patient's Age	Years	N/A
Sex	Patient's Gender	N/A	F=female M=male
Hgt	Patient's Height	Centimetres	N/A
Wgt	Patient's Weight	Kilograms	N/A
Proc	Surgical Procedure	N/A	0=Coronary Artery Bypass Graft (CABG) 1=Valvular Surgery 2=Combined CABG and Valvular Surgery 3=Atrial Myxoma Excision
HB	Pre-operative Haemoglobin	Grams per litre	N/A
Temp	Baseline Temperature	Degrees Centigrade	N/A

Variable Name	Variable Label	Units	Variable Values
Smoke	Smoking History	N/A	0=Never 1=Previous 2=Active
PackYr	Pack Years Smoked	Years	N/A
Cess	Time since cessation of smoking	Months	N/A
Device HB1	Novel Device Haemoglobin (1)	Grams per litre	N/A
Device HB2	Novel Device Haemoglobin (2)	Grams per litre	N/A
Device HB3	Novel Device Haemoglobin (3)	Grams per litre	N/A
Device HB4	Novel Device Haemoglobin (4)	Grams per litre	N/A
BGA Hb1	Blood Gas Analyser Haemoglobin (1)	Grams per litre	N/A
BGA Hb2	Blood Gas Analyser Haemoglobin (2)	Grams per litre	N/A
BGA Hb3	Blood Gas Analyser Haemoglobin (3)	Grams per litre	N/A

Variable Name	Variable Label	Units	Variable Values
BGA Hb4	Blood Gas Analyser Haemoglobin (4)	Grams per litre	N/A
FBC Hb1	Full Blood Count Haemoglobin (1)	Grams per litre	N/A
FBC Hb2	Full Blood Count Haemoglobin (2)	Grams per litre	N/A
FBC Hb3	Full Blood Count Haemoglobin (3)	Grams per litre	N/A
FBC Hb4	Full Blood Count Haemoglobin (4)	Grams per litre	N/A
HB coeff1	Haemoglobin coefficient (1)	N/A	N/A
HB coeff2	Haemoglobin coefficient (2)	N/A	N/A
HB coeff3	Haemoglobin coefficient (3)	N/A	N/A
HB coeff4	Haemoglobin coefficient (4)	N/A	N/A

No	Age	Sex	Hgt	Wgt	Proc	HB	Temp	Smoke	PackYr	Cess
1	71	F	156	56	1	14.1	36	1	20	408
2	65	M	177	81.4	1	14.6	36	0	0	0
3	59	M	161	147.4	1	16.3	36	1	58.75	1.5
4	34	M	165	79.8	1	15.3	36.6	0	0	0
5	70	M	172	88	2	13.3	36.8	0	0	0
6	80	F	161.5	65.6	1	11.9	36	0	0	0
7	71	M	171	67	0	13	36	0	0	0
8	71	F	155	58	1	12	36	0	0	0
9	67	F	152	91.6	1	14.7	36	0	0	0
10	74	M	163.5	84.1	0	15.2	36.2	0	0	0
11	78	M	158	80	0	12.9	36.4	0	0	0
12	80	M	179	75	0	14.8	37	1	2	732
13	54	M	167.3	95.2	0	11.4	36.2	1	45	1.75
14	57	F	163	74.2	1	13.5	36.8	0	0	0
15	49	F	163	68	3	13.1	36.5	0	0	0
16	67	F	159	57.4	0	13.1	36	0	0	0
17	55	M	184	92.3	0	15.9	36.5	0	0	0
18	55	M	170	80.8	0	15.2	36.5	1	7.5	18
19	72	M	180	76.5	0	12.4	36.2	1	22.5	120
20	74	M	168	72.8	0	11	36.1	1	1	480
21	62	M	177.8	93.6	0	15.3	36.4	2	84	0
22	78	F	157.9	51	2	11.9	36.1	0	0	0
23	47	M	170	97.6	0	13.9	36.5	1	2.5	12
24	66	F	160	80	2	12.3	36.4	0	0	0
25	74	M	175.3	90	1	13.1	36.1	1	40	96

No	Dev Hb1	Dev Hb2	Dev Hb3	Dev Hb4	BGA Hb1	BGA Hb2	BGA Hb3	BGA Hb4
1	13.2	15.6	11.4	14	12.9	14.1	8.4	9.5
2	12.1	13	15.5	15.5	13.4	13.4	10.5	11.6
3	12.8	13.8	12.7	11.8	14.9	14.5	11.4	11.6
4	14.9	12.7	10.2	12.4	12.8	12.3	8.3	8.9
5	15.2	13.3	10.3	10.2	12.1	11.7	8.1	N
6	11.4	N	12.4	11.8	12.4	N	8.5	8.9
7	12	13.9	12.6	12.4	11.3	11.4	8	8.7
8	11.6	12	9.7	12.2	10.3	10.2	6.9	6.8
9	12.6	13.8	13.1	12.3	13.1	13.3	9.3	9.1
10	13.4	11.7	11.8	N	12.7	13.1	9.2	N
11	10.3	12.9	12.3	11.8	11	10.6	8.1	8.4
12	14.8	13.8	9.7	10.5	13	12.9	10.5	10.6
13	19	15.5	13.6	13.2	11.7	11.8	8.5	9.3
14	11.7	17.9	16.5	15.6	11.7	10	7.7	7.7
15	12.9	14	13.2	17.9	11.2	11.4	6	8.2
16	9.7	9.2	14	12	11.1	9.9	7	7.5
17	16	13.7	12.1	10.9	13.6	13.9	9.4	10.4
18	13.8	11.9	18.5	11.6	13	13.6	9.9	10.8
19	10.1	12.1	13.3	8.8	11.4	10.8	6.5	8.6
20	11.4	12.4	11.6	8.2	9.9	9.8	6.7	7.6
21	18.5	15.4	10.7	11.3	13	13.4	10.2	11.3
22	14.4	13.5	12.4	9.5	9.7	9.7	6.7	8.1
23	13.5	14.5	13.8	12.4	13.4	13.3	9	10.3
24	12	12.3	12.7	11.2	11.3	11.1	7.5	8.6
25	18.5	13.9	14	14.2	12.5	12.6	9.1	9.1

No	FBC Hb1	FBC Hb2	FBC Hb3	FBC Hb4	HB coeff1	HB coeff2	HB coeff3	HB coeff4
1	12.8	13.9	8.3	9.2	2.5	N	1.7	1.6
2	13	13.1	10.4	11.2	1.1	0.45	N	N
3	14.2	13.8	11	11.3	N	N	0.8	1.5
4	13.1	12.6	8.3	8.7	N	N	N	N
5	11.8	11.5	8.4	9.7	N	N	N	N
6	12	N	7.6	8.4	1.5	N	1.1	1.4
7	10.9	11.1	7.8	8.9	N	2.2	1	1
8	9.8	9.7	6.6	6.5	N	1.8	N	N
9	12.9	12.7	9.1	N	1	1.8	N	N
10	13.3	12	9.8	N	1.5	1.6	1.7	N
11	10.9	10.9	7.9	8	2.1	1.4	2	N
12	13	13	10.3	10.5	2.6	1.3	N	N
13	11.4	11.2	8.7	9	1.2	1.1	N	N
14	N	10.1	7.6	7.2	N	N	N	N
15	11.1	11.3	6.3	8.3	N	N	2.5	1.7
16	11.5	9.7	7.2	7.7	N	N	1.7	1.8
17	13	13.4	9.7	10.2	2.1	1	0.9	0.8
18	13	13	10	11.1	N	N	N	N
19	10.8	10	7.1	8.2	2.2	1.9	2.4	N
20	9.3	9	7	7.6	2.2	1.8	N	N
21	12.8	12.5	9.9	11.1	1.1	1.3	N	N
22	9	9.1	6.5	8.1	1.8	2.3	2.1	2.2
23	12.8	12.4	8.9	9.6	N	N	N	N
24	10.5	10.7	7.2	8.1	N	N	N	N
25	11.6	12	8.7	8.9	1.9	1.9	2	N

8.6.Data Set for Study II

Key to Data Set

N = data missing

N/A = variable has no units or value is continuous/not defined

Variable Name	Variable Label	Units	Variable Values
No	Patient Number	N/A	N/A
Hgt	Patient's Height	Centimetres	N/A
Wgt	Patient's Weight	Kilograms	N/A
BMI	Patient's Body Mass Index	Kilograms per metre squared	N/A
Dev Hb	Device Haemoglobin	Grams per litre	N/A
FBC Hb	Full Blood Count Haemoglobin	Grams per litre	N/A
Smoke	Smoking History	N/A	0=Never 1=Previous 2=Active
Cigs	Number of cigarettes per day smoked	N/A	N/A
Cess	Time since cessation of smoking	Months	N/A

Variable Name	Variable Label	Units	Variable Values
Temp	Temperature	Degrees Centigrade	N/A

No	Hgt	Wgt	BMI	Dev Hb	FBC Hb	Smoke	Cigs	Cess	Temp
1	160	63.4	25.00	12.60	10.90	1	10	120	N
2	160	64.0	25.00	17.80	11.20	0	0	0	36.8
3	159	67.7	26.80	17.50	11.30	0	0	0	36.7
4	161	67.2	25.90	15.90	12.30	1	10	3.46	36.9
5	164	104.9	39.00	17.50	11.60	0	0	0	36.7
6	164	71.9	26.80	17.50	11.10	0	0	0	36.6
7	164	73.6	27.40	13.50	11.30	0	0	0	36.8
8	164	58.1	21.60	13.70	11.70	1	5	48	36.5
9	158	56.8	22.80	17.50	12.40	0	0	0	37.0
10	170	59.0	20.40	13.30	11.60	0	0	0	36.6
11	175	72.0	23.50	13.60	12.20	0	0	0	36.9
12	154	61.2	25.80	11.70	11.50	0	0	0	36.7
13	165	59.1	21.70	14.10	11.10	1	10	4.62	36.7
14	162	53.0	20.20	16.80	11.10	0	0	0	36.6
15	172	69.9	23.70	16.70	10.00	1	10	5	36.6
16	174	74.1	24.40	15.60	12.80	1	10	108	36.5
17	173	63.0	23.10	16.00	12.40	0	0	0	37.1
18	N	N	24.40	13.50	11.30	0	0	0	N
19	168	76.0	27.10	12.10	12.30	0	0	0	N
20	165	84.1	28.30	13.30	11.30	2	6	0	N
21	163	95.8	33.50	13.50	12.70	1	N	108	N
22	178	76.7	23.00	13.00	12.50	0	0	0	N
23	157	78.0	31.60	12.00	13.40	0	0	0	N
24	160	67.0	26.20	13.10	11.40	0	0	0	N
25	155	64.0	26.40	14.10	12.20	1	N	96	N
26	158	78.6	29.90	12.40	11.60	0	0	0	N
27	170	114.9	37.60	13.00	11.80	0	0	0	N
28	168	64.0	22.60	12.00	10.70	0	0	0	N
29	150	62.5	27.80	12.20	12.00	0	0	0	N
30	159	87.9	37.10	12.00	11.80	0	0	0	N
31	163	84.4	31.60	13.90	11.40	2	3	0	N
32	170	73.7	24.60	13.50	9.60	0	0	0	N
33	165	69.0	25.30	12.20	13.20	2	5	0	N
34	168	78.7	26.70	12.20	10.80	0	0	0	N

No	Hgt	Wgt	BMI	Dev Hb	FBC Hb	Smoke	Cigs	Cess	Temp
35	158	58.9	23.40	11.20	10.80	2	10	0	N
36	161	59.0	22.80	13.40	12.20	1	N	4	N
37	168	71.7	24.50	12.50	10.70	2	10	0	N
38	154	49.0	20.70	11.60	11.40	0	0	0	N
39	152	74.0	31.20	13.70	10.90	0	0	0	N
40	161	52.2	19.80	12.60	10.60	0	0	0	N
41	162	69.9	26.70	11.20	12.30	2	2	0	N
42	170	68.0	23.50	12.30	12.90	1	6	48	N
43	166	84.0	32.30	13.80	12.10	2	8	0	N
44	161	72.5	28.10	13.60	9.90	0	0	0	N
45	171	61.5	21.10	11.70	11.60	1	1	6	N
46	171	70.3	24.10	13.80	12.50	0	0	0	N
47	171	87.3	29.80	13.50	11.90	0	0	0	N
48	161	62.0	23.90	11.30	13.30	1	1.5	36	N
49	152	61.4	25.90	13.20	11.80	1	3	6	N
50	163	55.6	21.10	11.30	11.80	0	0	0	N
51	161	70.0	27.00	10.70	10.60	1	20	72	N
52	161	92.2	35.60	14.10	11.50	0	0	0	N
53	172	80.5	27.20	12.90	12.40	0	0	0	N
54	162	59.8	22.90	12.70	11.80	0	0	0	N
55	165	86.0	31.60	11.10	11.30	0	0	0	N
56	166	65.2	23.60	11.40	9.90	0	0	0	N
57	169	72.2	25.20	13.50	12.70	0	0	0	N
58	163	62.0	23.50	10.60	10.90	0	0	0	N
59	166	62.6	22.70	11.10	10.90	0	0	0	N
60	157	72.2	29.30	12.20	11.40	2	3	0	N
61	168	82.2	29.30	12.20	11.50	0	0	0	N
62	162	70.0	26.70	13.20	13.00	0	0	0	N
63	153	84.0	35.90	10.80	12.20	0	0	0	N
64	166	63.8	23.30	12.00	10.20	0	0	0	N
65	156	72.9	29.90	12.20	12.80	0	0	0	N
66	168	64.9	22.60	11.80	10.80	0	0	0	N
67	165	65.3	24.00	12.50	10.40	0	0	0	N
68	177	75.0	23.90	12.40	11.50	0	0	0	N

No	Hgt	Wgt	BMI	Dev Hb	FBC Hb	Smoke	Cigs	Cess	Temp
69	165	101.8	37.50	11.10	11.90	0	0	0	N
70	162	60.6	23.10	10.50	12.20	0	0	0	N
71	167	97.1	35.10	11.60	10.10	1	8	6	N
72	166	76.0	27.60	11.20	13.30	1	N	192	N
73	170	93.2	32.20	10.40	13.20	0	0	0	N
74	161	101.0	39.00	12.80	12.80	1	10	5	N
75	158	58.3	23.20	11.60	11.50	0	0	0	N
76	168	66.0	23.40	11.10	7.50	2	10	0	N
77	155	58.1	24.40	11.10	11.00	0	0	0	N
78	164	83.6	31.10	11.80	11.50	0	0	0	N
79	156	72.0	29.60	10.80	12.20	1	N	120	N
80	163	74.4	27.10	10.90	12.10	1	10	24	N
81	167	75.0	27.10	13.60	12.00	0	0	0	N
82	175	80.0	26.10	12.10	12.70	1	10	36	N
83	166	70.0	25.40	12.80	13.00	1	1	6	N
84	154	58.0	24.50	11.40	12.60	0	0	0	N
85	176	80.0	25.80	11.70	12.50	0	0	0	N
86	176	96.3	31.10	11.20	12.70	0	0	0	N
87	163	68.0	25.60	10.80	13.20	1	5	5	N
88	172	73.0	24.70	10.90	11.70	1	20	12	N
89	168	86.0	30.50	13.90	13.40	1	10	4	N
90	167	94.0	32.90	12.40	12.40	0	0	0	N
91	161	82.9	31.90	12.80	11.10	1	N	180	N
92	178	105.7	33.40	12.30	11.90	1	N	10	N
93	176	88.3	28.70	13.00	14.00	0	0	0	N
94	168	62.2	22.20	12.10	10.40	2	6	0	N
95	159	77.2	30.50	10.40	10.40	1	1	24	N
96	163	72.4	27.10	11.20	11.00	1	20	24	N
97	161	63.2	24.40	13.10	11.80	0	0	0	N
98	161	62.9	24.30	12.00	10.20	2	3	0	N
99	168	95.0	33.70	11.80	13.10	0	0	0	N
100	157	59.4	24.30	11.10	10.70	1	N	120	N

8.7.Data Set for Study III

Key to Data Set

N = data missing

N/A = variable has no units or value is continuous/not defined

Variable Name	Variable Label	Units	Variable Values
No	Patient Number	N/A	N/A
Age	Patient's Age	Years	N/A
Sex	Patient's Gender	N/A	F=female M=male
Hgt	Patient's Height	Centimetres	N/A
Wgt	Patient's Weight	Kilograms	N/A
BSA	Patient's Body Surface Area	Metres squared	N/A
Proc	Surgical Procedure	N/A	0=Coronary Artery Bypass Graft 1=Mitral Valve Repair 2=Mitral Valve Replacement 3=Aortic Valve Replacement
Bolus	Volume of colloid administered	Millilitres	N/A

Variable Name	Variable Label	Units	Variable Values
HR1	Heart Rate at first reading pre-bolus	Beats per minute	N/A
HR2	Heart Rate at second reading pre-bolus	Beats per minute	N/A
HR3	Heart Rate at third reading pre-bolus	Beats per minute	N/A
HR4	Heart Rate at first reading post-bolus	Beats per minute	N/A
HR5	Heart Rate at second reading post-bolus	Beats per minute	N/A
HR6	Heart Rate at third reading post-bolus	Beats per minute	N/A
Sys1	Systolic blood pressure at first reading pre-bolus	Millimetres of Mercury	N/A

Variable Name	Variable Label	Units	Variable Values
Sys2	Systolic blood pressure at second reading pre-bolus	Millimetres of Mercury	N/A
Sys3	Systolic blood pressure at third reading pre-bolus	Millimetres of Mercury	N/A
Sys4	Systolic blood pressure at first reading post-bolus	Millimetres of Mercury	N/A
Sys5	Systolic blood pressure at second reading post-bolus	Millimetres of Mercury	N/A
Sys6	Systolic blood pressure at third reading post-bolus	Millimetres of Mercury	N/A
Dia1	Diastolic blood pressure at first reading pre-bolus	Millimetres of Mercury	N/A

Variable Name	Variable Label	Units	Variable Values
Dia2	Diastolic blood pressure at second reading pre-bolus	Millimetres of Mercury	N/A
Dia3	Diastolic blood pressure at third reading pre-bolus	Millimetres of Mercury	N/A
Dia4	Diastolic blood pressure at first reading post-bolus	Millimetres of Mercury	N/A
Dia5	Diastolic blood pressure at second reading post-bolus	Millimetres of Mercury	N/A
Dia6	Diastolic blood pressure at third reading post-bolus	Millimetres of Mercury	N/A
MAP1	Mean arterial pressure at first reading pre-bolus	Millimetres of Mercury	N/A

Variable Name	Variable Label	Units	Variable Values
MAP2	Mean arterial pressure at second reading pre-bolus	Millimetres of Mercury	N/A
MAP3	Mean arterial pressure at third reading pre-bolus	Millimetres of Mercury	N/A
MAP4	Mean arterial pressure at first reading post-bolus	Millimetres of Mercury	N/A
MAP5	Mean arterial pressure at second reading post-bolus	Millimetres of Mercury	N/A
MAP6	Mean arterial pressure at third reading post-bolus	Millimetres of Mercury	N/A
CVP1	Central venous pressure at first reading pre-bolus	Millimetres of Mercury	N/A

Variable Name	Variable Label	Units	Variable Values
CVP2	Central venous pressure at second reading pre-bolus	Millimetres of Mercury	N/A
CVP3	Central venous pressure at third reading pre-bolus	Millimetres of Mercury	N/A
CVP4	Central venous pressure at first reading post-bolus	Millimetres of Mercury	N/A
CVP5	Central venous pressure at second reading post-bolus	Millimetres of Mercury	N/A
CVP6	Central venous pressure at third reading post-bolus	Millimetres of Mercury	N/A
CI1	Cardiac index at first reading pre-bolus	Litres per minute per metre squared	N/A

Variable Name	Variable Label	Units	Variable Values
CI2	Cardiac index at second reading pre-bolus	Litres per minute per metre squared	N/A
CI3	Cardiac index at third reading pre-bolus	Litres per minute per metre squared	N/A
CI4	Cardiac index at first reading post-bolus	Litres per minute per metre squared	N/A
CI5	Cardiac index at second reading post-bolus	Litres per minute per metre squared	N/A
CI6	Cardiac index at third reading post-bolus	Litres per minute per metre squared	N/A
CO1	Cardiac output at first reading pre-bolus	Litres per minute	N/A
CO2	Cardiac output at second reading pre-bolus	Litres per minute	N/A
CO3	Cardiac output at third reading pre-bolus	Litres per minute	N/A

Variable Name	Variable Label	Units	Variable Values
CO4	Cardiac output at first reading post-bolus	Litres per minute	N/A
CO5	Cardiac output at second reading post-bolus	Litres per minute	N/A
CO6	Cardiac output at third reading post-bolus	Litres per minute	N/A
SV1	Stroke volume at first reading pre-bolus	Millilitres	N/A
SV2	Stroke volume at second reading pre-bolus	Millilitres	N/A
SV3	Stroke volume at third reading pre-bolus	Millilitres	N/A
SV4	Stroke volume at first reading post-bolus	Millilitres	N/A

Variable Name	Variable Label	Units	Variable Values
SV5	Stroke volume at second reading post-bolus	Millilitres	N/A
SV6	Stroke volume at third reading post-bolus	Millilitres	N/A
Dev1	Device output at first reading pre-bolus	N/A	N/A
Dev2	Device output at second reading pre-bolus	N/A	N/A
Dev3	Device output at third reading pre-bolus	N/A	N/A
Dev4	Device output at first reading post-bolus	N/A	N/A
Dev5	Device output at second reading post-bolus	N/A	N/A

Variable Name	Variable Label	Units	Variable Values
Dev6	Device output at third reading post-bolus	N/A	N/A
Excl	Reason for exclusion (if applicable)	N/A	0=Developed atrial fibrillation, 1=Found to have severe tricuspid regurgitation, 2=Device froze, 3=Patient refused consent

No	Age	Sex	Hgt	Wgt	BSA	Proc	Bolus
1	73	F	161	61	1.64	0, 1	427
2	39	F	162	90	1.94	1	630
3	83	M	170	70	1.81	1	N
4	28	F	170	121	2.28	2, 3	847
5	65	M	162	79	1.84	0	551
6	60	F	163	65	1.70	3	455
7	66	M	175	82.6	1.98	0	578
8	65	M	167	79.4	1.88	0	555
9	80	M	172	72.5	1.85	0	507.5
10	67	M	N	N	N	N	N
11	56	M	172	108	2.19	0	756
12	64	F	159	66	1.68	0	461
13	76	F	164	75	1.82	2	523
14	62	M	179	105	2.23	0, 3	735
15	72	M	165	74	1.81	0	516
16	N	N	N	N	N	N	N
17	64	F	155	64	1.63	0	448
18	54	M	177	75	1.92	0	525
19	62	M	165	71	1.78	0	497
20	75	M	173	74	1.88	0	515
21	N	N	N	N	N	N	N
22	77	M	172	77	1.90	0, 1	539
23	64	M	170	80	1.92	0	560
24	65	F	163	96	2.01	0	672
25	55	M	187	81	2.06	0	567

No	HR1	HR2	HR3	HR4	HR5	HR6
1	58	57	58	65	68	57
2	76	64	63	95	77	75
3	N	N	N	N	N	N
4	89	88	86	78	79	78
5	59	59	56	53	52	51
6	45	45	44	44	42	42
7	61	62	63	61	63	64
8	65	64	63	57	58	58
9	60	61	63	63	62	65
10	N	N	N	N	N	N
11	74	74	74	74	80	79
12	54	54	55	77	71	60
13	70	72	70	70	70	70
14	52	51	52	61	56	60
15	53	52	53	53	50	48
16	N	N	N	N	N	N
17	67	73	69	70	69	69
18	43	43	42	43	43	43
19	81	81	79	80	81	79
20	54	53	52	56	57	55
21	N	N	N	N	N	N
22	74	74	74	74	74	74
23	74	78	77	77	75	76
24	53	51	51	50	48	50
25	45	39	39	39	38	38

No	Sys1	Sys2	Sys3	Sys4	Sys5	Sys6
1	125	131	118	109	125	101
2	130	99	95	125	134	117
3	N	N	N	N	N	N
4	87	85	78	94	86	83
5	108	103	89	78	74	70
6	105	105	107	126	104	103
7	80	79	78	89	88	100
8	105	101	99	95	97	91
9	109	103	96	89	86	84
10	N	N	N	N	N	N
11	104	101	103	110	128	117
12	112	105	109	121	140	123
13	121	111	107	142	134	125
14	116	117	121	123	120	118
15	137	133	130	156	146	138
16	N	N	N	N	N	N
17	126	135	140	142	140	133
18	98	92	87	99	95	90
19	169	158	148	123	121	116
20	158	156	149	128	125	121
21	N	N	N	N	N	N
22	113	110	108	109	104	99
23	126	109	119	126	136	132
24	123	119	115	124	121	114
25	114	115	123	105	101	98

No	Dia1	Dia2	Dia3	Dia4	Dia5	Dia6
1	70	74	67	63	72	55
2	81	53	50	76	75	65
3	N	N	N	N	N	N
4	50	47	47	54	51	49
5	28	53	48	42	40	38
6	43	44	45	83	87	87
7	40	40	33	48	47	54
8	60	58	57	54	52	53
9	49	45	42	43	41	40
10	N	N	N	N	N	N
11	59	58	58	63	77	67
12	51	29	51	57	71	59
13	66	61	60	75	70	67
14	59	58	60	64	62	61
15	65	63	63	72	69	64
16	N	N	N	N	N	N
17	69	75	76	73	72	70
18	55	52	48	55	53	50
19	93	90	86	72	71	69
20	73	73	70	61	60	59
21	N	N	N	N	N	N
22	49	48	47	51	48	46
23	74	61	69	70	78	75
24	60	58	57	59	57	51
25	59	55	59	47	44	43

No	MAP1	MAP2	MAP3	MAP4	MAP5	MAP6
1	91	97	84	81	94	73
2	101	70	56	92	93	87
3	N	N	N	N	N	N
4	60	60	57	64	62	59
5	68	70	62	55	52	49
6	64	64	66	95	93	93
7	52	51	49	60	59	70
8	76	74	72	69	68	67
9	72	65	63	60	60	59
10	N	N	N	N	N	N
11	73	72	73	78	93	85
12	71	67	70	82	98	84
13	85	78	79	100	93	89
14	77	78	80	86	81	80
15	91	85	86	105	96	90
16	N	N	N	N	N	N
17	89	95	98	98	96	92
18	72	69	64	73	70	66
19	124	117	111	94	92	89
20	107	105	101	86	84	82
21	N	N	N	N	N	N
22	73	72	70	73	70	66
23	93	77	87	90	101	97
24	82	79	77	82	80	73
25	77	73	79	64	61	59

No	CVP1	CVP2	CVP3	CVP4	CVP5	CVP6
1	4	6	4	5	5	5
2	12	10	10	14	16	16
3	N	N	N	N	N	N
4	13	11	11	N	15	14
5	N	N	N	10	10	11
6	11	11	11	15	14	13
7	8	7	7	8	7	8
8	14	13	14	15	15	15
9	5	4	4	6	6	6
10	N	N	N	N	N	N
11	12	12	12	13	14	14
12	12	12	12	14	14	14
13	8	9	8	12	11	11
14	9	9	9	10	11	11
15	11	11	10	11	11	11
16	N	N	N	N	N	N
17	21	22	22	24	23	23
18	5	5	5	7	6	6
19	5	6	5	7	7	7
20	10	10	10	14	14	11
21	N	N	N	N	N	N
22	4	4	3	6	6	5
23	6	6	6	8	8	8
24	9	9	9	13	13	6
25	3	3	4	6	5	6

No	Cl1	Cl2	Cl3	Cl4	Cl5	Cl6
1	3.4	2.8	1.8	2.5	2.4	2.7
2	2.3	2.2	2.1	1.9	1.8	1.9
3	N	N	N	N	N	N
4	1.4	0.9	0.9	1.3	0.6	0.9
5	2.4	3.6	3	3.2	3.1	3.1
6	3.2	3.1	3.2	3.4	3.3	3
7	2.8	2.8	3	3	3.4	3.3
8	2.5	2.3	2.3	2.3	2.3	2.3
9	1.7	1.7	1.6	2	2	2
10	N	N	N	N	N	N
11	2.5	2.2	2.3	2	2	2.1
12	1.8	1.8	1.8	2.3	2.8	2.9
13	1.9	2.2	1.7	2.5	2.3	2.3
14	2.9	2.8	2.7	2.1	2.2	2.3
15	3.3	2.8	2.5	2.4	2.3	2.4
16	N	N	N	N	N	N
17	1.9	2	2	2	2.1	2.1
18	2	2	1.9	1.7	1.9	2
19	1.8	2	2	2.3	2.2	2.3
20	2.6	2.4	2.4	3.3	3.5	2.5
21	N	N	N	N	N	N
22	2.5	3.1	2.8	2.7	2.8	2.7
23	1.9	2	1.9	2.1	2.1	2.3
24	2.2	2.4	2.3	1.8	2	2
25	3.7	4.5	4.1	3	3.1	3.1

No	CO1	CO2	CO3	CO4	CO5	CO6
1	5.58	4.59	2.95	4.10	3.94	4.43
2	4.47	4.28	4.08	3.69	3.50	3.69
3	N	N	N	N	N	N
4	3.20	2.06	2.06	2.97	1.37	2.06
5	4.42	6.62	5.52	5.89	5.70	5.70
6	5.44	5.27	5.44	5.78	5.61	5.10
7	5.55	5.55	5.95	5.95	6.74	6.54
8	4.71	4.33	4.33	4.33	4.33	4.33
9	3.15	3.15	2.96	3.71	3.71	3.71
10	N	N	N	N	N	N
11	5.49	4.83	5.05	4.39	4.39	4.61
12	3.03	3.03	3.03	3.87	4.71	4.88
13	3.45	3.99	3.09	4.54	4.18	4.18
14	6.47	6.25	6.03	4.69	4.91	5.13
15	5.98	5.08	4.53	4.35	4.17	4.35
16	N	N	N	N	N	N
17	3.10	3.26	3.26	3.26	3.42	3.42
18	3.84	3.84	3.65	3.26	3.65	3.84
19	3.21	3.56	3.56	4.10	3.92	4.10
20	4.88	4.50	4.50	6.19	6.57	4.69
21	N	N	N	N	N	N
22	4.75	5.89	5.32	5.13	5.32	5.13
23	3.64	3.83	3.64	4.02	4.02	4.41
24	4.42	4.82	4.62	3.61	4.02	4.02
25	7.63	9.28	8.46	6.19	6.40	6.40

No	SV1	SV2	SV3	SV4	SV5	SV5
1	96.19	80.61	50.92	63.11	57.91	77.73
2	58.85	66.84	64.82	38.89	45.46	49.26
3	N	N	N	N	N	N
4	35.92	23.36	23.90	38.06	17.34	26.35
5	74.84	112.26	98.56	111.08	109.68	111.83
6	120.96	117.18	123.71	131.44	133.65	121.50
7	91.02	89.55	94.42	97.52	107.01	102.24
8	72.49	67.73	68.81	76.05	74.74	74.74
9	52.49	51.63	47.05	58.81	59.76	57.00
10	N	N	N	N	N	N
11	74.14	65.24	68.21	59.31	54.86	58.33
12	56.05	56.05	55.03	50.23	66.31	81.27
13	49.28	55.48	44.09	64.84	59.66	59.66
14	124.48	122.54	115.89	76.84	87.68	85.56
15	112.90	97.64	85.53	82.11	83.41	90.66
16	N	N	N	N	N	N
17	46.20	44.64	47.22	46.55	49.59	49.59
18	89.25	89.25	86.81	75.86	84.79	89.25
19	39.59	43.99	45.11	51.22	48.39	51.87
20	90.36	84.98	86.61	110.59	115.23	85.30
21	N	N	N	N	N	N
22	64.21	79.62	71.91	69.34	71.91	69.34
23	49.18	49.11	47.26	52.24	53.63	57.97
24	83.33	94.47	90.54	72.27	83.65	80.30
25	169.65	238.07	216.91	158.71	168.32	168.32

No	Dev1	Dev2	Dev3	Dev4	Dev5	Dev6	Excl
1	0.92	0.55	3.53	1.51	1.13	3.48	N/A
2	0.37	2.75	3.22	0.35	0.26	0.29	N/A
3	N	N	N	N	N	N	0
4	N	N	N	N	N	N	1
5	0.24	0.09	8.79	7.92	7.85	7.45	N/A
6	N	N	N	N	N	N	N/A
7	4.11	3.91	4.10	3.62	3.72	2.85	N/A
8	0.73	0.77	0.82	0.79	0.71	0.76	N/A
9	N	N	N	N	N	N	N/A
10	N	N	N	N	N	N	2
11	2.44	2.47	2.43	1.73	1.59	0.43	N/A
12	3.94	3.36	3.09	2.70	1.76	2.59	N/A
13	3.14	3.41	3.16	0.44	0.67	1.56	N/A
14	4.58	4.87	3.80	3.92	3.80	3.93	N/A
15	0.52	0.49	0.45	0.76	0.84	0.77	N/A
16	N	N	N	N	N	N	3
17	0.24	0.23	0.22	0.38	0.36	0.55	N/A
18	6.47	7.33	6.92	6.36	6.87	0.29	N/A
19	0.35	0.33	0.30	0.38	0.37	0.37	N/A
20	0.37	0.29	0.22	0.81	0.71	0.76	N/A
21	N	N	N	N	N	N	3
22	2.42	2.99	3.21	0.86	1.02	1.38	N/A
23	0.42	0.65	0.33	0.27	0.30	0.33	N/A
24	7.43	7.62	7.48	6.90	6.92	6.85	N/A
25	4.26	0.97	0.43	0.93	0.70	0.99	N/A